

STUDIES IN BICYCLIC COMPOUNDS

Thesis presented to the University of Glasgow

for the degree of Ph.D.

by

Richard Terence Wall, B.Sc.

1967

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I have just received your letter of the 10th inst. and am
glad to hear that you are well and happy. I am
also well and hope to hear from you again soon.

To

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Myrett

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ACKNOWLEDGEMENTS

I should like to thank Dr. G.L. Buchanan and Professor R.A. Raphael, F.R.S., for their constant encouragement and advice during the course of this research.

My thanks are also due to the staff of the departments responsible for recording high-resolution infra-red, proton magnetic resonance, and mass spectra, and micro-analyses.

The work described in this thesis was performed during tenure of a Research Scholarship awarded by the Carnegie Trust for the Universities of Scotland (1964-67).

SUMMARY

Part I : Synthetic approaches to allohimachalol

2-(δ -formylbutyl)-2,6,6-trimethylcycloheptanone was synthesised in six steps from tetrahydroeucarvone. Attempts to effect aldol cyclisation to 1,5,5,8-tetramethylbicyclo (4.4.1) undec-7-en-11-one, which has already been related to the naturally occurring sesquiterpene alcohol allohimachalol, were unsuccessful.

Other approaches afforded a variety of compounds, in particular, a number of bicyclo (4.3.1) decanes derived from 1,5,5-trimethyl-8-oxabicyclo (5.4.0) undec-6-en-9-one.

Part II : Studies in the 3-azabicyclo (3.3.1)nonane system

The reported procedure for the syntheses of a small number of 6-substituted 1,5-dinitro-3-methyl-3-azabicyclo (3.3.1)non-6-enes was extended to provide a wide range of 6- and 7-substituted analogues, the structures of which have been rigorously proved by chemical and spectroscopic methods.

Initial difficulty in assigning certain NMR signals of these compounds led to a study of the NMR shifts of protons α and β to the nitrogen atom in simple amines and amine picrates. Some correlation between structure and magnitude of shift was observed.

The scope of the reaction sequence leading to these compounds

was thoroughly investigated, and a number of 3-unsubstituted, 3-ethyl, and 3-benzyl analogues prepared. In particular, this made available several 3-substituted 1,5-dinitro-3-azabicyclo (3.3.1)nonan-7-ones, IR studies of which established the absence of interaction between the amine and carbonyl functions.

Evidence was presented confirming reported findings of the chair-chair conformation of the 3-azabicyclo (3.3.1)nonane system.

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PART I

SYNTHETIC APPROACHES TO ALLOHIMACHALOL

INTRODUCTION

Organic chemistry has gained much from the study of bridged bicyclic molecules, but in the main, attention has been focussed on the naturally occurring bicyclo (2.2.1) heptane and bicyclo (3.1.1) heptane systems; larger ring systems have received less attention, owing to a scarcity of synthetic methods. In particular, there is difficulty in constructing a bridge of more than three carbon atoms, e.g. in the preparation of a bicyclo (4.n.1) alkane from a (n+3)-membered cycloalkanone (1). Hence although closely related in structure, bicyclo (4.3.1) decanes (2) and bicyclo (4.4.1) undecanes (3) differ markedly in frequency of occurrence in the literature.

A survey of the methods available for preparations of bicyclo (4.3.1) decanes and bicyclo (4.4.1) undecanes reveals that there are four general routes, designated A,B,C and D.

Method A involves ring expansion of a suitable fused bicyclic system, of which there are three versions (a)-(c), as shown in Scheme 1. The following examples illustrate its application to the syntheses of bicyclo (4.3.1) decanes and bicyclo(4.4.1) undecanes.

Vogel et al.¹ have reported the synthesis of (4), which behaves as the bicyclo (4.4.1) undecane aromatic compound 1,6-methanodecapentaene¹ (4a). This is an example of the norcaradiene-cycloheptatriene equilibrium. Also known is its negatively charged bicyclo (4.3.1) analogue, the decatrienyl anion (5).² Analogues of

(4) occur in the steroid field. Treatment of 19-hydroxy-androst-4-ene-3,17-dione (6) with the amine (7) afforded³ the two 5,19-cyclosteroids (8) and (9). The latter was converted into the bicyclo (4.4.1) undecane steroid (10).

Likewise, Dauben and Laug⁴ observed that treatment of trans-8-hydrindanylcarmbylamine (11) with nitrous acid produced a mixture containing 6% bicyclo (4.3.1) decan-1-ol(12). Similar results were obtained with trans-9-decalylcarmbylamine (13). Although in this case details were not given,^{4,5} one product would be bicyclo (4.4.1) undecan-1-ol (14), probably in the cis and trans forms, since Eliel⁶ attributed both to Dauben and Westman (via a private communication).

A novel skeletal rearrangement in the steroid field has recently been observed.⁷ 6 β -bromo-4 β ,5-epoxy-5 β -cholestan-3 β -ol(15) when treated under reflux with lithium aluminium hydride in tetrahydrofuran formed 92% of 4,5-seco-4,6-cyclo-6 β -cholestan-3 β ,5 α -diol (16), a 6,10-cis-bicyclo (4.3.1) derivative with ring-B constrained in the boat conformation.

In method B, a cyclodecane or cyclononane compound undergoes a transannular reaction (Scheme 2). Westman and Stevens⁸ obtained from the solvolysis of 6-methylene-cyclodecyl tosylate (17) a mixture of 93% cis-bicyclo (4.4.1) undecan-1-ol (14), and 7% of an olefin fraction, the main component of which had a GLC retention time identical with

bicyclo (4.4.1) undec-1-ene(18). Comparison was obviously available with work done by Dauben, Westman and Bond,⁵ which has not been fully described.

Several transannular reactions of this type were observed by Buchanan et al.⁹ (vide infra), e.g., purification of the cyclononene gem-diester (19) by chromatography caused partial conversion to the bicyclo (4.3.1) ketoester (20).

The remaining two methods, C and D, may be considered together. They have been applied to the syntheses of bicyclo-(4.3.1) decanes, but not to the syntheses of bicyclo (4.4.1) undecanes. Basically, they consist either of attachment of a three carbon chain to a cycloheptane ring and subsequent ring closure (method C), or the opposite process, viz., condensation of a four carbon unit to a cyclohexane ring (method D). In two examples of D, bis-1,3-condensation to the cyclohexane ring yielded the bicyclo (4.3.1) decane in one step.

The first example of method C was reported by Prelog et al.¹⁰ in 1949. Condensation of 2-carbethoxycycloheptanone with 1,3-dichlorobut-2-ene afforded 1-carbethoxy-1-(3-chlorobut-2-enyl) cycloheptanone (21), which was cyclised with concentrated sulphuric acid (with prior formation of the 3-ketobutyl derivative, a reaction discovered by Wichterle¹¹) to 1-carbethoxy-7-methylbicyclo(4.3.1) dec-7-en-10-one (22). Hydrolysis and decarboxylation led to 7-methylbicyclo (4.3.1)

dec-7-en-10-one (23). Removal of the carboethoxy group from (21) was found to cause cyclisation in the alternative way to form the ~~enone~~ (24).

A method discovered in 1956 by Stork and Landesman¹² for preparing bicyclic aminoketones by condensation of acrolein with the pyrrolidine enamines of cyclopentanone and cyclohexanone was used by Gritter et al.¹³ to prepare 7-pyrrolidinobicyclo (4.3.1) decan-10-one (25) from the pyrrolidine enamine of cycloheptanone. Later investigations on this reaction by Schut and Liu¹⁴ included the preparation of the related 7-(4-phenyl-1-piperazyl) bicyclo (4.3.1) decan-10-one (25a).

In 1963, Sands¹⁵, using the Wichterle reaction, synthesised bicyclo (4.3.1) dec-7-en-10-one (26) from 2-carbethoxy cycloheptanone, or, more economically, from cycloheptanone, and 1,3-dichloropropene, followed by cyclisation of the resultant 2-(3-chloroallyl)-cycloheptanone (27, 27a) with concentrated sulphuric acid. The use of 1,3-dichloropropene instead of 1,3-dichlorobut-2-ene (vide infra) for the preparation of bicyclic compounds offers the same advantages of an allyl halogen for the alkylation of the carbethoxycycloalkanone, together with a vinyl halogen, inert in the initial alkylation, but available for the later sulphuric acid-induced cyclisation. Furthermore, 2-(3-chloroallyl) cycloheptanone does not have a methyl group available for reaction with the carbonyl group when the carboethoxy group

(as in 27a) is absent, and the alternative mechanism of ring closure is therefore not available.

The same author¹⁶ prepared 1-carboxybicyclo (4.3.1) dec-7-en-10-one (28) from 2-carbethoxy cycloheptanone by means of the method used by Cope and Synerholm¹⁷ to synthesise the analogous bicyclo (3.3.1) compound from acrolein and 2-carbethoxycyclohexanone. Hydrogenation converted (28) to 1-carboxybicyclo (4.3.1) decan-10-one (29).

During their investigations on reactions involving bridge scission of bridged ring systems, Buchanan et al.⁹ condensed acrolein with 2-carbethoxy-7-methylcycloheptanone (30) to obtain the bicyclic alcohol (31), but all attempts to dehydrate this to (20) yielded the tetralin acid (32) as the only recognisable product.

The preliminary stages of a stereoselective hydroazulene synthesis by Marshall and Partridge¹⁸ involved condensation of 2-carbethoxycycloheptanone with methyl vinyl ketone, and ring closure with sulphuric acid to yield (22), the same compound prepared by Prelog et al.¹⁰. Elaboration to the saturated alcohol (33), followed by solvolysis of the mesylate (33a), afforded the hydroazulene (34) in 80% yield.

The bridged ketol (35) was obtained in 8% yield as a side-product from the cyclisation of the trione (36), (prepared by condensation of methyl vinyl ketone with 2-methylcycloheptane-1,3-dione),

with pyrrolidine and acetic acid to the enedione (37)¹⁹.

The first example of route D to bicyclo (4.3.1) decanes was due to Opitz and Mildenberger²⁰, who in 1961 prepared the ketones (38; 15%) and (39; 31%) by refluxing 1,4-diiodobutane and o-xylylene bromide respectively with the pyrrolidine enamine of cyclohexanone and ethyldicyclohexylamine in acetonitrile. The ketone (38) was very slightly contaminated with (40), and another product in this reaction was the dione (41). However, similar treatment of cycloheptanone enamine yielded no bicyclo (4.4.1) undecanones, only starting material being obtained.

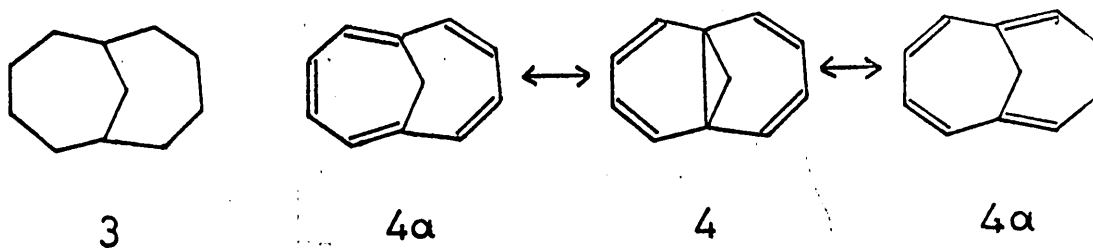
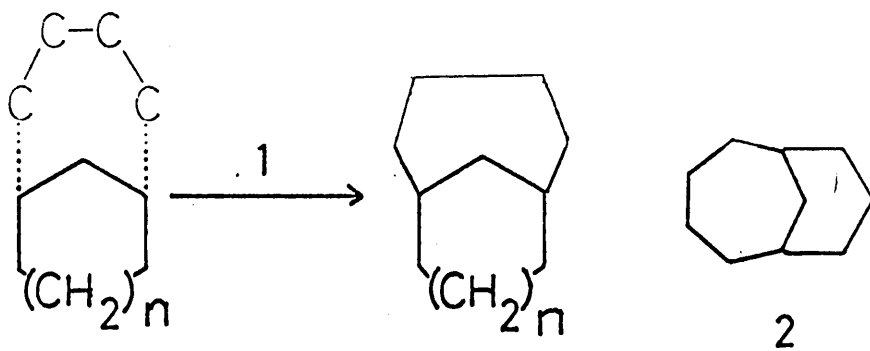
Sands¹⁶ reacted 2-carbethoxycyclohexanone with 1,4-dichlorobut-2-ene to obtain crude (42) in low yield. Hydrolysis and hydrogenation furnished the ketoacid (29), which he obtained by an independent synthesis (vide supra).

As proof of the aforementioned steroid rearrangement, Collins et al.⁷ treated the tosylate (43), prepared from cholest-4-en-3-one, with potassium t-butoxide to form in low yield the ketone (44), the main product being the cyclic enol ether (45). Another recent synthesis, due to Loewenthal²¹, involved the cyclisation of the cyclohexenone acid (46) by refluxing with 2-naphthalene sulphonic acid in toluene to the bicyclic enedione (47) in only 8% yield, although analogous bicyclo (3.2.1) octanes and bicyclo (3.3.1) nonanes were formed in 80-91% and 70% yields respectively.

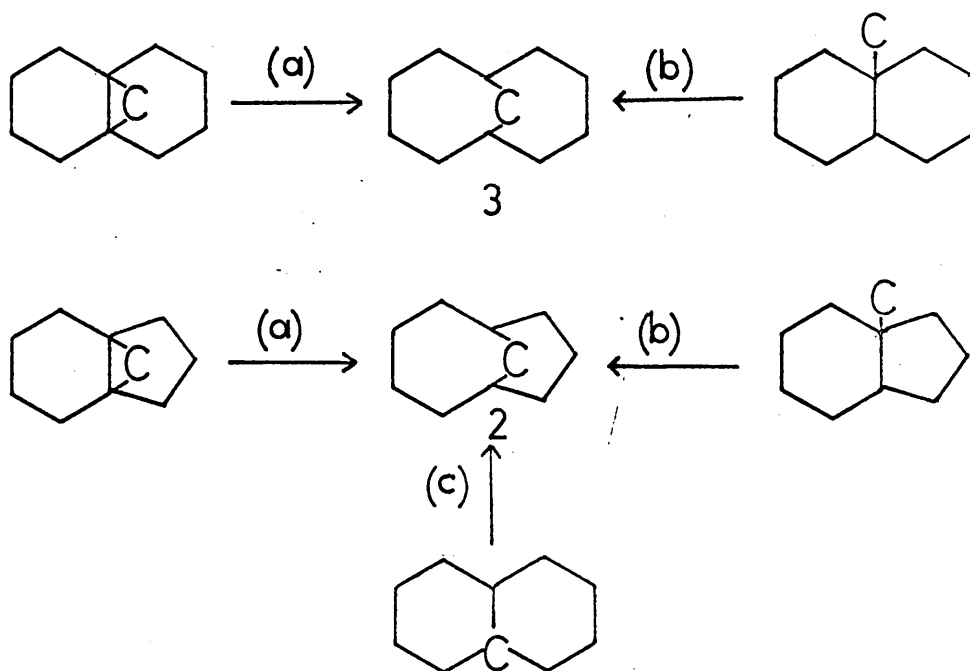
It can be seen from the above survey that there is no preparative route to bicyclo (4.4.1) undecanes.

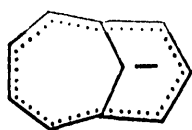
No bicyclo (4.3.1) decane has been isolated from natural sources. In contrast however, Bisarya and Sukh Dev²², investigating the alcohol fraction (15%) of the essential oil from Himalaya deodar (Cedrus deodara, Loud.) found it to contain two new sesquiterpene alcohols, himachalol (48) (41%) and allohimachalol (30%), the latter possessing the bridged bicyclo (4.4.1) undecane structure (49), a new type in sesquiterpenoids. It was postulated²² to have arisen from the species (50)²³, the biogenetic precursor of himachalenes, longiborneol and related compounds. This was confirmed by solvolysis of allohimachalol tosylate to yield α -himachalene (51; 3%), β -himachalene (52; 15%), himachalol (48; 24%) and allohimachalol (34%), (Scheme 3). The only possible structures for allohimachalol were hence (49), (53) and (54). Spectroscopic and chemical evidence ruled out (53) and (54). The solvolysis experiment also permitted the unequivocal assignment of the configuration of the hydroxyl group, and since the absolute configuration of the himachalenes and himachalol have been established²⁴, allohimachalol must have the absolute stereostructure (49).

Because of the novel structure of allohimachalol (49), the absence in the literature of a planned synthetic route to a bicyclo (4.4.1) undecane, and the interest in this department in bridged bicyclic systems²⁵, a synthetic sequence from carvone (55) aimed at allohimachalol was undertaken.

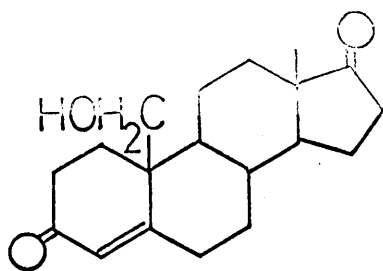


SCHEME 1

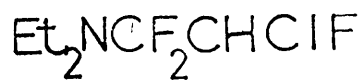




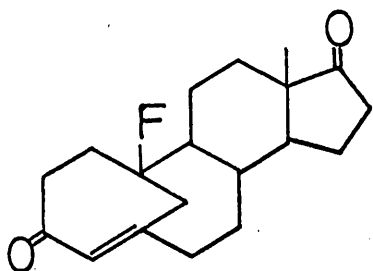
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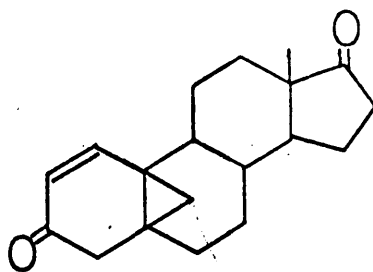
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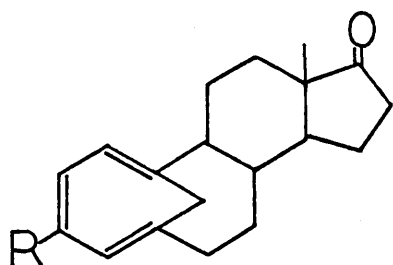
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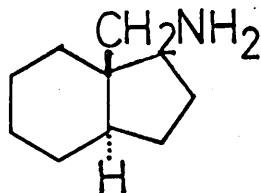
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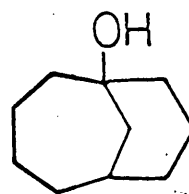
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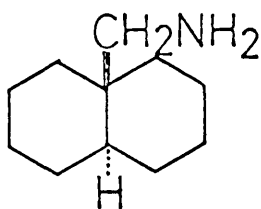
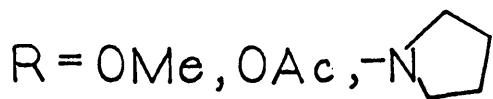
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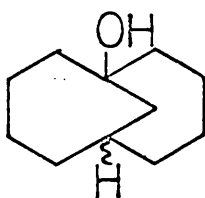
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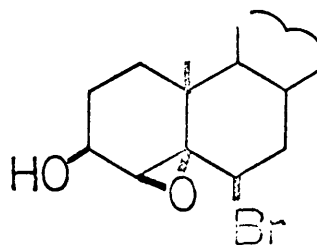
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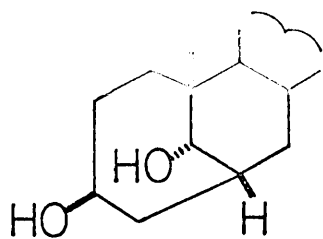
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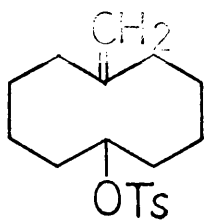
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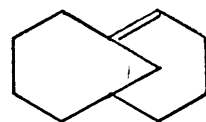
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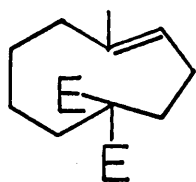
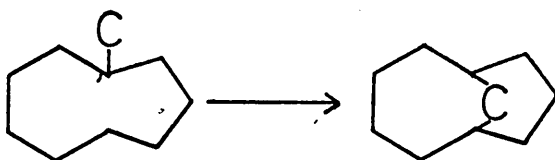
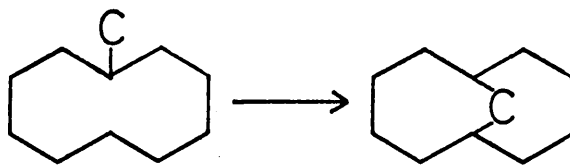


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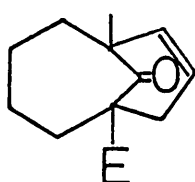


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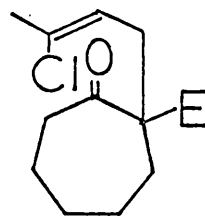
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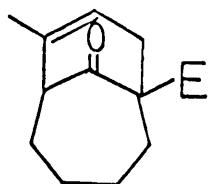


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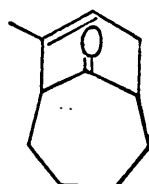


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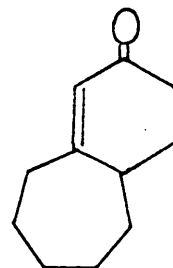
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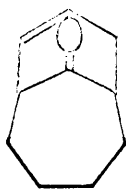
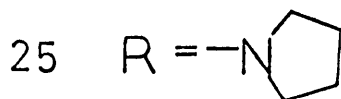
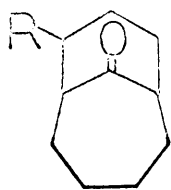
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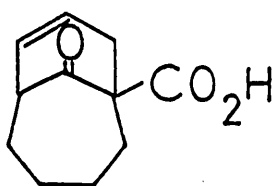
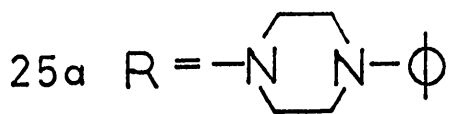
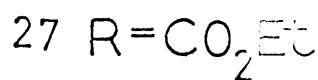
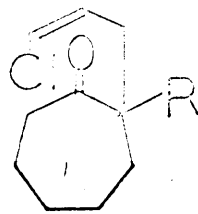
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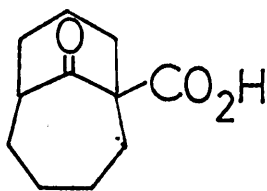
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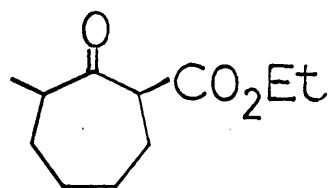
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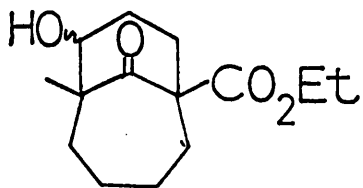
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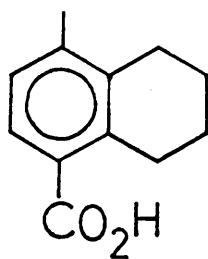
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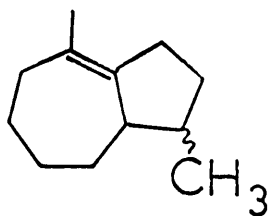
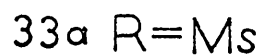
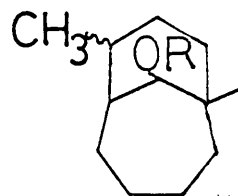
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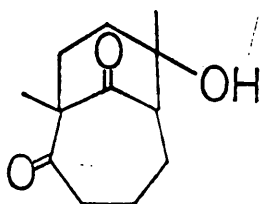
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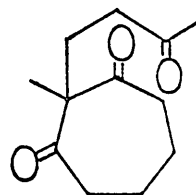
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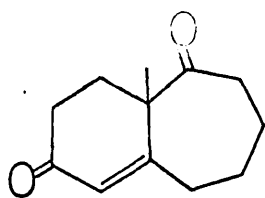
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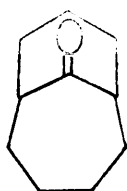
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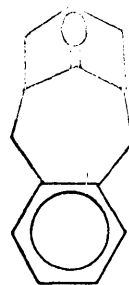
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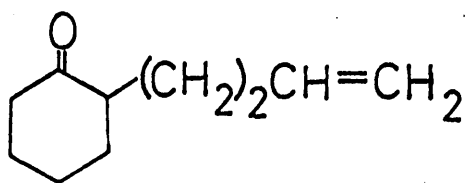
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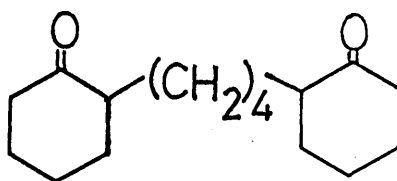
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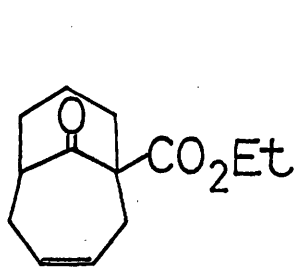
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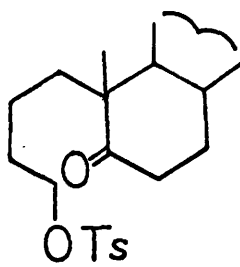
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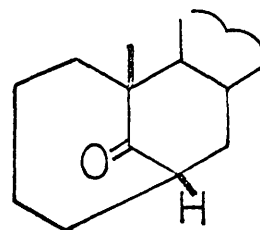
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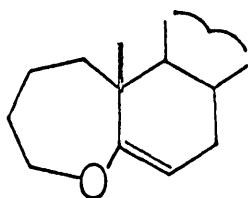
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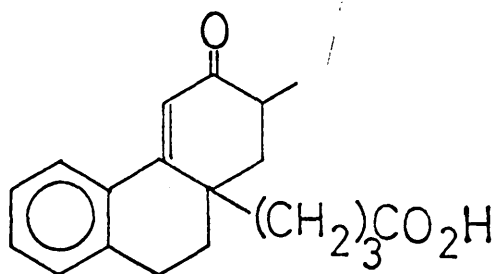
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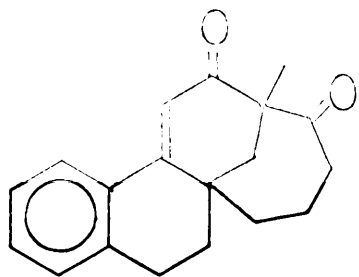
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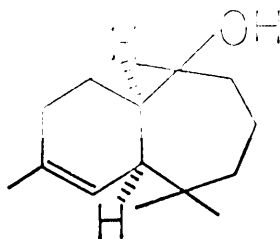
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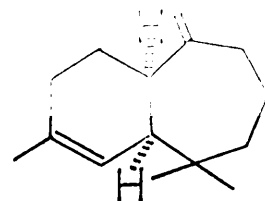
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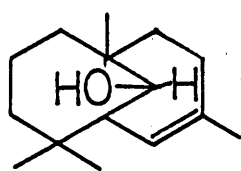


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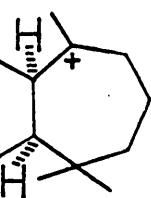
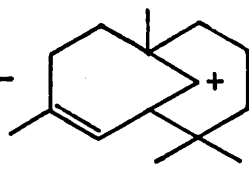


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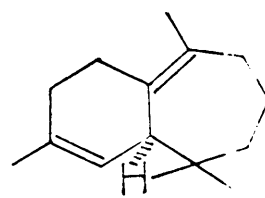
SCHEME 3



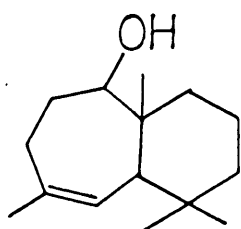
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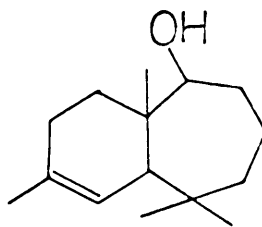
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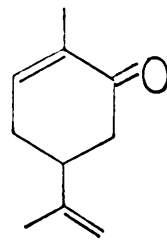
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DISCUSSION

The readily available monoterpene carvone (2) was selected as the starting material for a synthetic route to allohimachalol (1), the only known naturally occurring bicyclo (4.4.1) undecane. The long-known conversion of carvone (2) to eucarvone (3) could then be utilised, followed by hydrogenation to the saturated cycloheptanone, tetrahydroeucarvone (4), (Scheme A). The sequence then required would be essentially the attachment of a four-carbon bridge to this ketone in the 2,7-positions (Scheme B). It was anticipated that this would be a difficult task, for all syntheses of the analogous bicyclo (4.3.1) decane system by elaboration of a cyclohexanone have proceeded in low yield (see introduction).

It was therefore decided to use as an intermediate the 1,5-dione (10), the proposed sequence to which involved the facile attachment of a three-carbon side chain to the 2-position of tetrahydroeucarvone (Scheme C). Condensation of (4) with acrylonitrile and hydrolysis of the resultant ketonitrile (5) would afford the ketoacid (6), cyclisation and concomitant dehydration of which would then yield the δ -enol lactone (7). By analogy with other enol lactones, it was thought that (7) would react with a methyl Grignard reagent to form the bicyclic ketol (9), convertible to the desired dione (10) by a retro-aldol process. Since the side chain carbonyl group of (10) would be less hindered than the ring carbonyl, treatment with the Wittig reagent methoxymethylenetriphenylphosphorane would furnish the enol

ether (25) of the ketoaldehyde (48). By cyclisation of the side chain of (48), the required bicyclic skeleton would be obtained, in the form of the enone (50), (Scheme D), which was prepared by Bisarya and Sukh Dev²² by oxidation of allohimachalol.

An alternative route to the key intermediate (48) envisaged elaboration of the enone (13), an aldol product of (10). Treatment of the enone (13) with methylenetriphenylphosphorane would produce the diene (41). It was hoped that advantage could be taken of the higher reactivity of the exocyclic double bond to reduce (41) selectively to the olefin (44), oxidative cleavage of which, by ozonolysis or by osmium tetroxide and sodium periodate, would then yield (48). (Scheme E).

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Carvone (2) was brominated and dehydrobrominated to yield eucarvone (3) by the method of Wallach.²⁷ Hydrogenation to tetrahydroeucarvone (4) by the method of Barnes and Houlihan²⁸ proceeded in a higher yield than that reported. Tetrahydroeucarvone, a colourless, volatile oil, with a strong characteristic odour, had $\nu_{\text{C=O}}$ 1704 cm^{-1} . A feature of its NMR spectrum useful for structural confirmation of certain compounds derived from it was an AB quartet at 7.55 τ (2H, J = 11.5 c/s) due to the two non-equivalent C₇ protons.²⁹

Under strongly basic conditions, tetrahydroeucarvone underwent smooth cyanoethylation to afford 57% of a single product, which when purified was obtained as a colourless crystalline solid, C₁₃H₂₁ON, m.p. 44.5 - 46°. Its mass spectrum confirmed the molecular weight of 207, i.e. monocyanoethylation had occurred to form (5). The IR spectrum had peaks at 1703 (C=O) and 2255 cm^{-1} (C \equiv N), and in the NMR spectrum, an AB quartet at 7.55 τ (2H, J=11.5 c/s) demonstrated the absence of substitution at C₇.

Hydrolysis of the ketonitrile (5) by prolonged reflux with dilute hydrochloric acid in dioxan proceeded in almost quantitative yield to the ketoacid (6), a colourless solid, C₁₃H₂₂O₃. Its structure was rigorously confirmed spectroscopically as for (5).

Treatment of (6) with refluxing acetic anhydride, in the presence of sodium acetate^{30,25} afforded the δ -enol lactone (7), a distilled sample of which, a colourless viscous liquid, exhibited

absorption at 1758 (enol lactone $C=O$) and 1662 $cm.^{-1}$ ($C=C$) in the IR. A sharp singlet in the NMR spectrum at 4.73 τ was assigned to the olefinic proton. The material appeared to be hygroscopic, and a satisfactory analysis was not obtained. The mass spectrum however showed a molecular weight of 208.

The enol lactone (7) remained unchanged on exposure to a 0.5 M excess³¹ of methyl magnesium iodide for one hour. When subjected to a 5 M excess³² for three hours, at either room or reflux temperature, however, (7) was converted completely into a mixture of three compounds. Chromatographic separation afforded the most polar, predominant component, as a viscous colourless oil after distillation. NMR and mass spectroscopy showed it to be the ketol (8), and not the desired bicyclo (4.3.1) decanolone (9). The material had IR absorption at 1696 and 3610 $cm.^{-1}$, and weak, broad, concentration dependent absorption at 3530 and 3370 $cm.^{-1}$, assigned to an intermolecularly bonded hydroxyl. In the NMR spectrum, a quartet at 7.58 τ (2H, $J = 10.5$ c/s, C_7 protons) excluded the bicyclic structure (9); also observed were a singlet at 8.32 τ (hydroxyl proton), removed on adding D_2O , and a singlet at 8.80 τ (6H, side chain methyl protons), as well as the signals due to the C_2 - and C_6 -methyl protons. The mass spectrum had no molecular ion, but contained strong peaks at 222 (P-18, loss of H_2O) and 154 (P-86, loss of side chain) m/e . This latter peak was found to be common to

all compounds of this type, arising by loss of the side chain (table 5). These data fully confirmed structure (8).

That the desired 1,5- diketone (10) was an intermediate in this reaction was proved by its isolation from the above chromatogram in very low yield. Physical data were assembled later, when more material became available (vide infra).

Since the preparation of (10) from (7) was clearly impracticable, attempts were then made to find an alternative route from the ketonitrile (5) and the ketoacid (6). Considerable starting material was recovered by treatment of (5) with methyl magnesium bromide.³³

A complex mixture containing only a trace of unchanged (5) resulted when methyl magnesium iodide³³ was used. When reacted with methyl lithium,³³ the ketonitrile (5) yielded, on removal of acidic material, a mixture of three compounds. Separation by preparative TLC afforded the dione (10) in 29% yield. Unfortunately, the course of this reaction was not reproducible, and later runs gave distinctly lower yields (ca. 7%) of (10). This route to (10) could not therefore be regarded as suitable for inclusion in a synthetic plan.

Methyl ketones may also be prepared by the action of methyl lithium on acids.³⁴ Accordingly, the ketoacid (6) was refluxed for two hours with a 3M excess of this reagent. The product consisted almost entirely of unchanged acid, the small neutral fraction being a mixture of three components.

Another method which was considered was the reaction between

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dimethylcadmium and an acid chloride. However, attempts to prepare the acid chloride (11) by reacting the acid (6) with either thionyl chloride or oxalyl chloride led to mixtures of (11) and the enol lactone (7), the latter predominating. An odour of acid chloride was detectable in the product, which had IR absorption at 1700 (cycloheptanone C=O), 1800 (acid chloride C=O) and 1760, 1660 cm^{-1} (enol lactone absorptions). Also, the NMR spectrum was similar to that of pure (7).

Certain esters ~~are~~ convertible to β -ketosulphoxides by reaction with two equivalents of the sodium salt of dimethyl sulphoxide (dimesylsodium). Hydrogenolysis results in the formation of the corresponding methyl ketone. ³⁶ Treatment of the acid (6) with diazomethane gave in high yield the ester (12), which analysed for $\text{C}_{14}\text{H}_{24}\text{O}_3$, had $\nu_{\text{C=O}}$ 1698 (ketone) and 1742 cm^{-1} (ester), and a NMR singlet at 6.33 τ (3H, methyl ester protons). Only a low yield of neutral product, accompanied by much ketoacid (6), was obtained on reaction of (12) with dimesylsodium. It contained two compounds, and its IR spectrum was transparent in the carbonyl region.

A successful route to (10), practicable on a large scale, was finally achieved by condensation of tetrahydroeucarvone (4) and methyl vinyl ketone, with ethanolic potassium hydroxide as catalyst. ³⁷ A 40% yield of (10) was realised, after distillation to remove unchanged (4), and chromatographic separation from a small quantity of the enone (13), formed by cyclisation of (10) in the basic medium. The

diketone (10) formed a mono-2,4-dinitrophenylhydrazone, $C_{20}H_{28}N_4O_5$, which had a single carbonyl peak in the IR at 1699 cm.^{-1} . Since the present dione had $\overset{CCl_4}{C=O}$ 1695 (cycloheptanone $C=O$) and 1721 cm.^{-1} (sidechain $C=O$), the more hindered ring carbonyl group had therefore been unaffected by 2,4-dinitrophenylhydrazine. The side chain methyl group gave rise to a singlet in the NMR at 7.89τ (δ). The molecular weight of 224 was confirmed by mass spectrometry.

With a practical route to (10) available, its elaboration to (48) could now be studied. However, simultaneously, it appeared of interest to investigate the potential of the readily obtainable enol lactone (7). This was prompted by the discovery in this department that compounds of this type, e.g., (14), undergo reductive rearrangement with lithium aluminium tri-(*t*-butoxy) hydride³⁸ to form bridged bicyclic ketols, e.g.,²⁵ (15). Similar treatment of the enol lactone (7) in THF at -70° afforded a mixture (in decreasing polarities) of the ketoacid (6), the bicyclic ketol (16), unchanged (7), and a small amount of a compound of unknown constitution. Chromatographic separation furnished 39% of the desired bicyclic ketol (16), obtained after distillation as a colourless crystalline solid, m.p. ca. $71-76^\circ$, which was not recrystallisable. Chromatography (TLC and GLC) indicated the presence of only one compound, later shown to be the axial alcohol (vide infra). Some later runs of this reaction gave material with

IR absorption identical to that of the axial ketol, but consisting of two compounds, the axial and equatorial epimers. The mass spectrum of axial (16) showed a molecular ion at $P=210$ m/e , with a peak at 192 m/e (P-18; loss of H_2O). IR bands were observed at 1698 , 3615 and 3445 cm^{-1} , the last being the centre of broad, concentration dependent absorption, due to the intermolecularly hydrogen bonded hydroxyl group. The NMR spectrum showed a broad multiplet at 5.50 τ (1H, half-band width ca. $9c/s$, C7 carbonyl proton, i.e., the C7 hydroxyl group must be axial³⁹), a doublet at 7.78 τ (1H, $J=3.5c/s$, C6 proton), a singlet at 8.1 τ (hydroxyl proton), which disappeared on addition of D_2O , as well as the signals due to the ring methylene protons, and the C1 and C5 methyl protons (Table 7).

The ketol (16) was further characterised by the preparations of the diol (17) and the ketotosylate (18). The diol was available in rather low yield by prolonged treatment of (16) with lithium aluminium hydride or lithium aluminium tri-(*t*-butoxy) hydride, followed by chromatographic removal from unchanged (16), which was always present. This reflected the lack of reactivity of the C10 carbonyl group, which is discussed below. The diol (17), $C_{13}H_{24}O_2$, with m.p. $91-97^\circ$ (C_{10} epimeric mixture), had $\nu_{max}^{CCl_4}$ 3625 (free hydroxyl) and $3550-3200$ cm^{-1} (intermolecularly bonded hydroxyl). The presence of two hydroxyl groups was shown by the NMR spectrum, in which the C7 and C10 carbonyl protons absorbed as a triplet at

6.32 τ ($J=5\text{c/s}$) and a doublet at 6.45 τ ($J=2.5\text{c/s}$) respectively.

Treatment of the ketol (16) with tosyl chloride in pyridine produced the ketotosylate (18), m.p. 111-115°, which analysed for $\text{C}_{20}\text{H}_{28}\text{O}_4\text{S}$. Spectral data were completely compatible with structure (18). In particular, the NMR spectrum contained a broad multiplet at 4.80 τ (1H, half-band width ca. 8c/s, C₇ carbonyl proton, i.e., the C₇ tosyloxy group must be axial³⁹) and the mass spectrum, although containing no molecular ion, showed a peak at 192 m/e ($P=172$, loss of p-toluenesulphonic acid).

The C₇ -axial conformation of (18), and therefore (16), was confirmed by the conversion of (18) by refluxing ethanolic sodium ethoxide⁴⁰ to the unconjugated enone (19) in good yield. This compound, an extremely volatile oil with a camphoraceous odour, had a mass spectral molecular weight of 192. The vinylic protons gave rise to a NMR multiplet at 4.13 τ (2H, half-band width 5c/s), showing that, as expected by Bredt's rule,⁴¹ the double bond was unconjugated. Also observed were two unresolved doublets at 7.45 τ (C₆ proton) and 7.72 τ (C₉ protons, J ca. 2c/s). $\nu_{\text{max}}^{\text{CO14}}$ were observed at 3030 (=C-H str.) and 1708 cm^{-1} (C=O), and $\nu_{\text{max}}^{\text{CS2}}$ at 764 and 694 cm^{-1} (=C-H def.). The UV spectrum had $\lambda_{\text{max}}^{\text{EtOH}}$ 226m μ , fairly typical absorption for a β,δ -unsaturated ketone.⁷⁰

⁴² Oxidation of the ketol (16) by chromium trioxide in sulphuric acid gave the dione (20) in high yield. A twin carbonyl band was

observed in the IR spectrum (in CCl_4), at 1722 and 1696 cm^{-1} . Although this doublet is explicable on the basis of cyclohexanone and cycloheptanone carbonyl frequencies respectively, compounds similar to (20), incorporating a non-enolisable cyclic β -diketone moiety are known to exhibit a twin IR carbonyl peak.^{40,43} Of the two explanations of this phenomenon, Fermi resonance and vibrational coupling, the latter has been preferred. In the case of the dione (20), the possibility that Fermi resonance might be the cause of the doublet carbonyl was excluded by the observation that the peak separation ($\Delta\nu = 25 \text{ cm}^{-1}$) was virtually unchanged in a series of solvents of differing polarities (Table 3). The dione formed a mono-2,4-dinitrophenylhydrazones, $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_5$, which had $\nu_{\text{C=O}}$ Nujol 1695 cm^{-1} , due to the unreacted bridge carbonyl group. In the NMR spectrum, the C_6 bridgehead proton gave rise to a singlet at 7.00 τ (1H), very slightly split, possibly by long range coupling with the C_4 protons or the C_5 methyl protons. Complex absorption at 7.2-7.5 τ (2H) was attributed to the C_3 protons. Mass spectrometry confirmed the molecular weight of 203.

Two attempts were made to effect a shorter route to (20) from the readily available ketoacid (5) and the ketoester (12). A mixture of the acid (5) and p-toluenesulphonic acid in tetralin was heated at reflux in a Dean-Stark water separator.⁴⁴ The product, although almost entirely non-acidic, consisted of a complex mixture.

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Marshall and Scanio prepared the bicyclo (5.3.1) undecane dione (21) by cyclisation of the ketoester (22) with sodium hydride in refluxing 1,2-dimethoxyethane. However, similar treatment of the ketoester (12) afforded mainly the acid (6), and none of the dione (20) was detectable in the neutral fraction.

Before a practicable route to (10) had been discovered, it was realised that the bicyclic dione (20) could be of use in the preparation of (10). The C₁₀ carbonyl group of (20), known to be unreactive, should remain unaffected by a methyl Grignard reagent, and the resultant ketol (9) convertible to (10) by a retro-aldol process. In the event, exposure of (20) to excess methyl magnesium iodide furnished a mixture of unchanged (20), the two epimeric ketols (9), and the diol (23). The formation of this complex mixture made it apparent that the synthesis of (10) by this method was not **feasible**, and with the IR and NMR spectral characterisation of the crystalline diol (23) completed, attention was turned to the behaviour of (20) under the following conditions. Reaction with methanolic base gave only the ketoacid (6). The alternative cyclononanone acid (24), which would result by attack at the bridge carbonyl, was not formed. Sodium borohydride reduction of (20) furnished a mixture of the C₇ epimers of (16), the composition being 1:1 (estimated by integration of the GLC peaks). Furthermore, the epimer with the lower retention time was shown by GLC to be identical to the axial

ketol (16) obtained by complex hydride reduction of the enol ketone (7).

Cyclic ketones, particularly cyclohexanones, are known to 46
undergo ring enlargement with diazomethane or substituted diazomethanes.
However, rigorous examination (by IR, NMR, TLC and GLC) of the products
obtained by treatment of (20) with nitrosoethylurethan in ethanolic
ether in the presence of sodium carbonate, 47,48 or with ethereal
diazomethane, 47 or with ethereal diazoethane, 48 revealed only the
presence of unchanged dione (20).

Hence although the studies of these bicyclo (4.3.1) decanes
made no tangible contribution to the synthesis of the bicyclo (4.4.1)
undecane (1), it was felt that the chemical and spectroscopic information
derived from them would be invaluable when the desired analogous bicyclo
(4.4.1) undecane system came to be investigated.

As planned, (10) was reacted with methoxymethylenetriphenyl-
phosphorane 49,50, initially at -70°, then at room temperature; the
product was largely unchanged (10), with small amounts of triphenyl-
phosphine oxide (Ph₃PO) and two compounds, one slightly less polar, the
other more polar, than (10). Removal of unchanged (10) by distillation,
and of Ph₃PO by chromatography, left material in which no enol ether
(25) could be detected. Several attempts under more forcing conditions
gave similar results, and it became evident that this route to (48),
(Scheme D), would have to be abandoned.

Consequently, several alternative sequences to (48) were explored. Theoretically, a four carbon side chain could be constructed by Amdt-Eistert homologation⁵¹ of the ketoacid (6) to the ketoacid (26), but, in practice, the required acid chloride (11) could not be prepared pure. (vide supra).

Ring-opening addition reactions between various nucleophilic reagents and cyclopropane compounds substituted at the same ring carbon by two electron - withdrawing groups, (Scheme F), , have long been known.⁵² It was envisaged that alkylation of (27) with the 2-carbanion of tetrahydroeucarvone would yield the ester (28) with the requisite four carbon side chain. However, attempts to synthesise (27) by condensation of ethylene dibromide and diethyl malonate⁵³ or ethyl cyanoacetate⁵⁴ gave in every case only the unreacted active methylene compounds, the boiling points of which are similar to those reported for the desired cyclopropanes. The products were identified by their IR spectra, and by the absence of signals in the NMR spectra at ca. 8.7 and 8.4 τ , characteristic of the cyclopropyl protons⁵⁵ of (27, R=CO₂Et) and (27, R=CN) respectively.

Claisen ester condensations have been reported⁵⁶ between dialkoxyacetate esters (29) and esters to form dialkoxy- β -ketoesters (30), which have been hydrolysed by base to α -ketoacetals (31). An analogous reaction between the ketoester (32) and ethyl diethoxyacetate (29, R=Et) would produce the β -ketoester (33), convertible by base to

(34), which possesses a four carbon side chain. Accordingly, esterification of the ketoacid (6) gave the ethyl ester (32), which had $\nu_{\text{C=O}}^{\text{CCl}_4}$ 1699 (ketone) and 1737 cm^{-1} (ester), and the following signals in the NMR spectrum: a quadruplet at 5.83 τ (2H, $J=7\text{c/s}$, carbethoxy methylene protons), a triplet at 8.76 τ (3H, $J=7\text{c/s}$, carbethoxy methyl protons, and a quartet at 7.54 τ (2H, $J=11\text{c/s}$, C₇ protons). Exposure of (32) and ethyl diethoxyacetate (29, R=Et) to the forcing conditions described for (29, R=Me),⁵⁶ afforded a product, the neutral fraction of which consisted of unchanged (32). The fractions soluble in bicarbonate and hydroxide solutions were both acidic, none of the β -ketoester (33) being present.

Attention was then focussed on the second projected sequence to the ketoaldehyde (48), (Scheme E). The enone (13) was prepared in very high yield by aldol cyclisation of the 1,5-dione (10) with methanolic potassium hydroxide. In larger scale preparations, however, the crude product from condensation of (4) with MVK³⁷ (vide supra) was heated at reflux overnight with base. Distillation separated unreacted (4) from the enone (13), obtained in 65% yield as a viscous pale yellow oil, which usually slowly solidified, and could be recrystallised only with some difficulty. Its 2,4-dinitrophenylhydrazone, C₂₀H₂₆N₄O₄, was obtained as red needles. The $\alpha\beta$ -unsaturated double bond in (13) gave rise to IR absorption at 1671 (C=O) and 1613 cm^{-1} (C=C), and to UV absorption at $\lambda_{\text{max}}^{\text{EtOH}}$ 245 m μ (ϵ 15000).

A singlet in the NMR spectrum at 4.26 τ (1H) was ascribed to the vinylic proton.

Reduction of (13) with sodium borohydride afforded the allylic alcohol (35), distillation of which generated a small amount of a much less polar compound, probably the diene (36) (vide infra). Separation from (36), followed by cold recrystallisation, furnished (35) as colourless needles with melting pt. 83-85°. Principal IR peaks were at 3610 (free hydroxyl), 1670 (C=C), 1024 (C-O) and 782 and 761 cm^{-1} (=C-H def.). The 60 Mc/s NMR spectrum exhibited a singlet at 8.25 τ (hydroxyl proton), removeable by D₂O exchange, and a broad multiplet at 5.7 τ (1H, C₉ carbinyll proton). In their synthesis of thujopsene, Dauben and Ashcraft⁵⁷ obtained the two allylic alcohols (37a) and (37b) by reduction of the enone (38). The C₇ olefinic proton, by coupling with the adjacent C₈ carbinyll proton, gave rise to doublets at 4.63 τ (J=1.3 c/s) and 4.48 τ (J=4.5 c/s) for the β -alcohol (37a) and the α -alcohol (37b) respectively.⁵⁸ In agreement with this, Finnegan and Bachman found that the pertinent signal in the allylic alcohol (39) at 4.55 τ appeared to be only very weakly split (J = 1-2 c/s). On this basis, (39) was confidently assigned the quasi-equatorial configuration. In the case of (35), the 60 Mc/s spectrum contained a very slightly split (J ca. 1.5 c/s) doublet for the C₈ olefinic proton at 4.67 τ (1H), suggesting that the hydroxyl group was quasi-equatorial, i.e., β . This was confirmed by the

100 Mc/s spectrum, in which the broad multiplet at 5.81 τ due to the C₉ carbonyl proton became a triplet (J=8c/s) on irradiation of the C₈ proton signal. The value of J was of the order expected for diaxial coupling between the C₉ proton and the C₁₀ protons.⁵⁹

The olefinic proton signal in this spectrum was a broad singlet (half-band width 5c/s) at 4.76 τ , which was distinctly narrowed (half-band width 3c/s) by irradiation of the C₉ proton signal.

The mass spectrum of (35) showed no molecular ion, but a peak at 190 m/e (P-18) indicated facile dehydration.

That the contaminant in the distilled sample of the alcohol (35) (see p22) was indeed the diene (36) was proved by the dehydration of (35) to (36) in high yield by polyphosphoric acid. The diene (36) exhibited identical TLC behaviour to the distillation contaminant.

Furthermore, UV absorption at $\lambda_{\text{max}}^{\text{EtOH}}$ 273 m μ (10300) confirmed the presence of a homoannular diene. In the IR spectrum, there was weak absorption at 3025(=C-H), 1645 and 1590 cm.⁻¹ (C=C), and strong absorption at 700 cm.⁻¹ (=C-H def.).

Since under basic conditions, only the enone (13) was formed by cyclisation of (10), it was decided to attempt the preparation with acidic reagents of the alternative product, the bicyclo (4.3.1) decenone (40). A mixture of unchanged dione (10) and enone (13), together with a trace of a less polar compound, was obtained on treatment of (10) with p-toluenesulphonic acid (PTSA) in refluxing benzene,⁶⁰ or

toluene, (in this case no starting material remained), or with concentrated sulphuric acid.⁶¹ The least polar compound was isolated in the first two cases, but IR spectroscopy demonstrated that neither was the desired enone (40). Only the enone (13) was found to be present after prolonged reflux with boron trifluoride etherate.⁶² These attempts to cyclise (10) served however to provide valuable experience in the later cyclisation experiments on the ketoaldehyde (48).

The next step in the route to (48), (Scheme E), was the preparation of the diene (41). This was obtained as a colourless, mobile liquid in 69% yield after chromatography, by reaction of (43) with methylenetriphenylphosphorane.^{49,63} Initially, the crude reaction products were chromatographed on silica, which achieved good separation. However, one sample was completely isomerised during chromatography to material with only very weak double band absorption in the IR, and later runs were purified on neutral alumina. The diene (42), synthesised in a similar manner by Sondheimer and Mechoulam,⁶⁴ was isomerised by concentrated hydrochloric acid to the diene (43). Similar treatment of the pure diene (41) furnished material with IR absorption identical to that of the isomerised chromatography product. The diene (41) appeared to undergo very gradual atmospheric oxidation to the enone (13), and was not obtained analytically pure. Its mass spectrum however indicated the correct

molecular weight of 204, while UV absorption at $\lambda_{\text{max}}^{\text{EtOH}}$ 243 m μ (ϵ 17800) and IR absorption at 3075, 1632, 1598, 894 and 865 cm.⁻¹ proved the presence of the diene grouping. Olefinic proton signals in the NMR spectrum were observed as a sharp singlet at 4.17 τ (1H, C₈ proton), and a broad singlet at 5.30 τ (2H, exomethylene protons).

Hydrogenation conditions were next required to accomplish selective reduction of the exocyclic double bond of (41). In their synthesis of patchouli alcohol, Büchi and MacLeod⁶⁵ employed a similar sequence, viz., enone (45a) to olefin (45c) via the diene (45b). The hydrogenation step was carried out with Raney nickel W2 in ethyl acetate. De Graw and Bonner⁶⁶ converted (46a) to (46e) via (46b), the last stage being achieved with 10% palladium on charcoal in ethyl acetate. After testing a variety of catalyst-solvent combinations, smooth hydrogenation to the olefin (44) was found to occur in 93% yield with 5% palladium on charcoal in ethyl acetate. The resultant colourless, volatile oil was shown to have the requisite Δ^7 double bond by its NMR spectrum, which showed a doublet at 4.77 τ (1H, J=3.5 c/s) for the C₈ olefinic proton, and no signal due to a vinylic methyl group. This latter fact ruled out the Δ^8 isomer. The C₉ methyl signal appeared to be at 8.93 τ , but its splitting pattern was not clearly visible due to neighbouring peaks. The IR spectrum was transparent in the 1650 cm.⁻¹ region (C=C str.),

but weak absorption at 875, 855 and 733 cm^{-1} was assigned to the trisubstituted double bond ($=\text{C}-\text{H}$ deformations). The molecular weight of 206 was confirmed by mass spectrometry.

Ozonolysis of the olefin (44) yielded a complex mixture, spectroscopic examination of which did not detect the presence of the desired ketoaldehyde (48). Recourse was then taken to an alternative cleavage procedure. Treatment of (44) with osmium tetroxide in pyridine, followed by decomposition of the osmate ester with an aqueous pyridine solution of sodium bisulphite,⁶⁷ furnished 94% of the cis-7,8-diol (47). The purified diol, a colourless crystalline solid, $\text{C}_{15}\text{H}_{28}\text{O}_2$, had two sharp bands in the IR spectrum at 3580 and 3637 cm^{-1} , which were attributed to the C_7 and C_8 free hydroxyl groups respectively. Important features of the NMR spectrum were a doublet at 6.59 τ (1H, $J=9\text{c/s}$, * C_8 carbinylic proton), a singlet at 8.20 τ (2H, hydroxyl protons), removed by addition of D_2O , and singlets at 8.83, and 9.01, 9.08 τ (12H, C_1 , C_9 and C_5 methyl protons respectively). The doublet expected for the C_9 methyl group probably coincided partially with the C_5 methyl signal.

The diol (47) was resistant to cleavage by excess sodium metaperiodate,⁶⁸ in dry or aqueous methanol, even with long reaction times. When lead tetraacetate⁶⁹ was employed, the diol was smoothly cleaved to give (after removal of a trace of acidic material) 93% of a neutral, pale yellow oil, which comprised mainly one compound,

* This value of J indicated that both the C_8 hydroxyl group and the C_9 methyl group are equatorial.

the ketoaldehyde (48). It exhibited IR carbonyl absorption at 1693 (ketone) and 1727 cm^{-1} (aldehyde). In addition, the C-H str. of the formyl group was responsible for a weak band at 2700 cm^{-1} . A doublet in the NMR spectrum at 0.37 τ (1H, $J=2\text{c/s}$) confirmed the presence of a formyl group with one adjacent proton, and a quartet at 7.59 τ ($J=11\text{c/s}$), caused by the two C_7 protons, was also present. The small acidic fraction was not investigated, but probably consisted of the ketoacid (49).

Cyclisation conditions were then required to convert the ketoaldehyde (48) to the known bicyclo(4.4.1)undecenone (50). It was considered that acidic reagents would accomplish this more readily than basic reagents, since the latter would tend to promote undesired condensations involving the aldehyde group. Indeed, treatment of the ketoaldehyde (48) with base furnished a complex of neutral compounds. Similar aldol cyclisations to form bridged bicyclic compounds have been executed by use of PTSA in refluxing benzene⁶⁰, or concentrated sulphuric acid^{17,61,71}. These reagents afforded the dehydrated aldol product. Others, such as acetic/dilute hydrochloric acids^{17,71} gave only the first-formed alcohol.

After several hours reflux with PTSA in benzene, (48) was only partially converted into three much less polar compounds. The incomplete reaction, and the complex product formed under these conditions, turned attention to the use of concentrated sulphuric acid. Under these more drastic conditions, similar complex mixtures were

however obtained, although no starting material was present.

The failure of this cyclisation step to afford smoothly the desired bicyclic skeleton could be attributed to three main factors. Steric hindrance by the C₆ gem-dimethyl group would discourage the desired reaction at C₇. The alternative mode of cyclisation to form a bicyclo(5.3.0)decane compound (Scheme G) might also occur. Lastly, several other side reactions would be possible owing to the reactive nature of the formyl group.

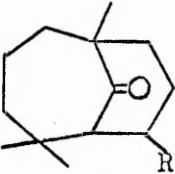
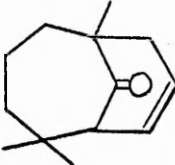
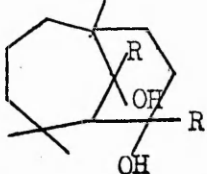
Table 1 Absorption frequencies in CCl_4 of some trimethylcycloheptanone compounds

compound	C-H def.					
	C=O str.	CH ₂ C-Me	C-Me	CMe ₂		
tetrahydro- eucarvone (4)	1704	1458	1388	1373,1367		
	R					absorption due to R
	CN	1703	1466	1388	1378,1367	2255 (C=N) str.
	CO ₂ H	1701	1466	1388	1375,1365	3300-2500(bonded OH), 1710(C=O)
	CO ₂ Et	1699	1464	1389	1375,1366	1737(C=O), 1186(C-O str.)
	CO ₂ Me	1698	1464	1388	1376,1366	1742(C=O), 1198(C-O str.)
	COCH ₃	1695	1464	1388	1374,1365	1721(C=O), 1352(C-H def.)
	CMe ₂ OH	1696	1464	1388	1374,1365	3610(free OH), 3530,3370* (bonded OH)
	Me CHCHO	1698	not measured			1727(C=O), 2710(C-H str. of CHO)

The chemical structure is a bicyclic ketone. It consists of a cyclooctane ring fused to a five-membered ring. The five-membered ring contains a carbonyl group (C=O) and a substituent 'R'. The cyclooctane ring has a methyl group at the bridgehead position adjacent to the carbonyl group.

* weak, broad absorption, decreasing on dilution (intermolecular hydrogen bond)

Table 2 Absorption frequencies in CCl_4 of some bicyclo(4.3.1) decane compounds

compound	R	C=O str.	C-H def.			other absorptions
			CH_2 C-Me	C-Me	CMe_2	
	OH	1698	1454	1389	1376, 1368	3615 (free OH), 3445 ^b (bonded OH)
	OTs	1702	1452	1390	c	1598, 1494 (ar. C=C), 1372, 1340 and 1187, 1174 (S=O str.), 908, 894 (=C-H def.)
	=O	1722 1696	1456	1391	1378, 1371	
		1708	1453	1390	1376, 1365	3030 (=C-H), 764, 694 ^a (=C-H def.)
	H		1466	1385	1363	3625 (free OH), 3200-3550 ^b (bonded OH)
	CH_3		1468	1382	1367	3615 (free OH), 3470 ^b (bonded OH)

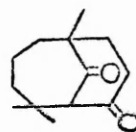
a. in CS_2

b. centre of broad, weak absorption, intensity decreasing on dilution (intermolecular hydrogen bond)

c. masked by SO_2 str. absorption

Table 3 Solvent dependence of the carbonyl stretching absorptions* of the dione (20)

Solvent	$\nu^1_{C=O}$	$\nu^2_{C=O}$	$\nu(\nu^1-\nu^2)$
Chloroform	1716	1691	25
Acetonitrile	1717	1692	25
Carbon tetrachloride	1722	1696	26
Cyclohexane	1724	1699	25



(20)

* concentrations: ca. 0.015M in 0.5mm. cells

Table 4 Absorption frequencies in CCl_4 of some bicyclo(5.4.0)undecane compounds

compound	R	C-H def. C-Me and CMe ₂	other absorptions
(13)	=O	1462, 1386, 1377, 1364	3020(=C-H), 1671(C=O), 1613(C=C)
(35)	OH	1458, 1380, 1359	3610(free OH), 1670(C=C), 782 and 761 ^a (C-H def.), 1024(C-O)
(41)	=CH ₂ ^b	1461, 1384, 1362	3075(=C-H), 1632, 1598(C=C), 894 and 865(C-H def.) ^b
(44)	CH ₃	1457, 1376, 1359	875, 855, 733(C-H def.) ^b
enol lactone(7)		1460, 1389, 1382, 1358	1758(C=O), 1662(C=C), 1260(=C-O), also 1213, 1174, 1099, 1065
diene (36)		1462, 1385, 1365	3025(=C-H), 1645w, 1590w(C=C), 700s(C-H def.)
diol (47)		1463, 1382, 1368	3637(free 2 ^y OH), 3580(free 3 ^y OH)

a. in CS₂

b. thin film

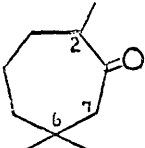
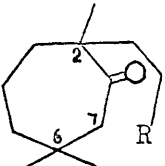
Table 5 Mass spectra of some compounds derived from tetrahydroeucarvone

compound	actual and obs. mol. wt.	loss of sidechain	loss of CH ₃ (15)	other peaks
ketonitrile (5)	207	154(loss of 53)	192	174(P-33)
ketoacid (6)	226	154(loss of 72)		208(loss of H ₂ O) 209(loss of OH) 193(P-33)
ketoester (32)	254	154(loss of 100)	239	221(P-33) 209(loss of OEt) 236(P-18)
ketoester (12)	240	154(loss of 86)	225	209(loss of OMe) 207(P-33) 222(P-18)
diketone (10)	224	154(loss of 70)	209	191(P-33)
ketol (8)	240 ^a	154(loss of 86)	207	189(P-33) 222(loss of H ₂ O)
enone (13)	206		191	178(loss of CH ₂ =CH ₂ or CO)
allylic alcohol (35)	208 ^a		175	190(loss of H ₂ O) 91(C ₇ H ₇ ⁺)
diene (41)	204		189	91(C ₇ H ₇ ⁺)
olefin (44)	206		191	91(C ₇ H ₇ ⁺)
enol lactone (7)	208		193	175(P-33)
diene (36)	190		175	91(C ₇ H ₇ ⁺)
diol (47)	240		225	222(loss of H ₂ O) 207(P-33)
bicyclic ketol (16)	210		195	192(loss of H ₂ O)
ketotosylate (18)	364 ^b		177	192(loss of PTSA) 172(PTSA)
bicyclic diketone (20)	208		193	
bicyclic enone (19)	192		177	
bicyclic diol (17)	212 ^a		179	194(loss of H ₂ O)

a. no molecular ion observed. Losses were calculated from the P-18 peak.

b. do., except P-172 peak.

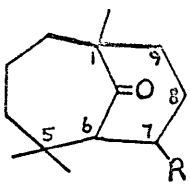
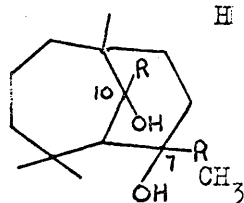
Table 6 NMR spectral assignments of tetrahydroeucarvone and some 2-substituted-2,6,6-trimethylcycloheptanones in CDCl_3

compound	t y p e o f p r o t o n				signals due to R
	C_7	$\text{C}_6\text{-Me}$	$\text{C}_2\text{-Me}$	ring and chain CH_2	
	7.55q $J=11\text{c/s}$	9.00s 9.05s	8.90d $J=7\text{c/s}$	8.45 ^a	
	R				
CN	7.55q $J=11.5\text{c/s}$	9.03s 9.10s	8.94s	8.45 ^a	
CO_2H	7.57q $J=11\text{c/s}$	9.03s 9.13s	8.98s	8.48 ^a	
CO_2Et	7.54q $J=11\text{c/s}$	9.02s 9.12s	8.98s	8.48 ^a	5.48q, 8.76t both $J=7\text{c/s}$
CO_2Me	7.57q $J=11\text{c/s}$	9.03s 9.13s	8.98s	8.48 ^a	6.33s
COCH_3	7.55q $J=11\text{c/s}$	9.03s 9.16s	9.01s	8.48 ^a	7.89s
CMe_2OH	7.58q $J=11\text{c/s}$	9.02s 9.12s	8.97s	8.57 ^a	8.32s(hydroxyl H) 8.80s(methyl H)
CH_2MeCHO	7.59q $J=11\text{c/s}$	9.03s 9.12s	8.97s	8.49 ^a	0.37d($J=2\text{c/s}$, formyl H) 8.86 ^b (methyl H)

a. broad singlet centred on broader absorption

b. possibly a doublet with $J=7.5\text{c/s}$, since a peak at 8.98, overlapped by the C_2 -methyl resonance, was detectable

Table 7 NMR spectral assignments of some bicyclo(4.3.1)decane compounds in CDCl_3

compound	t y p e o f p r o t o n			
	R	methyl	ring methylene	others
	OH	8.90s 8.92s 9.00s	8.48 ^a	5.50m ^b (C ₇ carbinyl H) 7.80d(J=3.5c/s, C ₆ H) 8.1s ^c (hydroxyl H)
	OTs	7.58s(aromatic) 8.91s(C ₁) 9.13(C ₅)	8.55 ^a	2.22d ^d , 2.66d(both J=8c/s) 4.80m ^b (C ₇ carbinyl H)
	=O	8.80s(C ₁) 8.95s(C ₅)	8.40 ^a	7.00s ^e (C ₆ H) 7.2-7.5 complex (C ₈ H)
	enone (19)	8.90s 9.00s	8.52 ^a	4.13m(olefinic H) 7.45 ^f (C ₆ H) 7.72 ^f (J ca. 2c/s, C ₉ H)
		H	9.03s 9.09s 9.16s	8.66 ^a
		8.75s, 8.77s (C ₇ and C ₁₀)	8.56 ^a	8.3s(hydroxyl H) ^c
		9.00s		
		9.04s		
		9.13s		

a. singlet centred on broad absorption

b. half-band width value proved the axial configuration of the group R (see discussion)

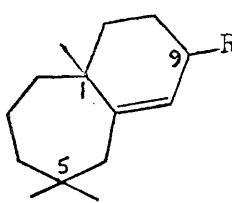
c. signal disappeared on addition of D_2O

d. two protons ortho to the oxygen atom in the Ts group; the other doublet due to the remaining two aromatic protons

e. very slightly split, possibly by long range coupling with C_4 or C_5 Me protons

f. poorly resolved doublet

Table 8 NMR spectral assignments of some bicyclo(5.4.0)undecane compounds in CDCl_3

compound	type of proton				
	R	methyl	ring methylene	olefinic	others
	=O	8.84s(C_1) 8.98s, 9.17s(C_5)	8.57 ^a	4.26s	
	OH	8.97s(C_1) 9.07s, 9.17s(C_5)	8.67 ^a	4.67d J ca. 1.5c/s ^b	5.7m(C_9 carb- inyl H) 8.25s ^c (hydrox- yl H)
	=CH ₂	9.00s(C_1) 9.05s, 9.17s(C_5)	8.66 ^a	4.17s(C_8) 5.30 broad s (exomethylene H)	
	CH ₃	9.00s(C_1) 9.07s, 9.15s(C_5) 8.93 ^d (C_9)	8.72 ^a	4.77d J=3.5c/s	
	enol lactone (7)	8.77s(C_1) 8.92s(C_5)	8.28 ^a	4.73s	
	diol (47)	8.93s(C_1 and C_9 ^d) 9.01s, 9.08s(C_5)	8.53 ^a		6.59d(J=9c/s) 8.20s ^c (hydrox- yl H)

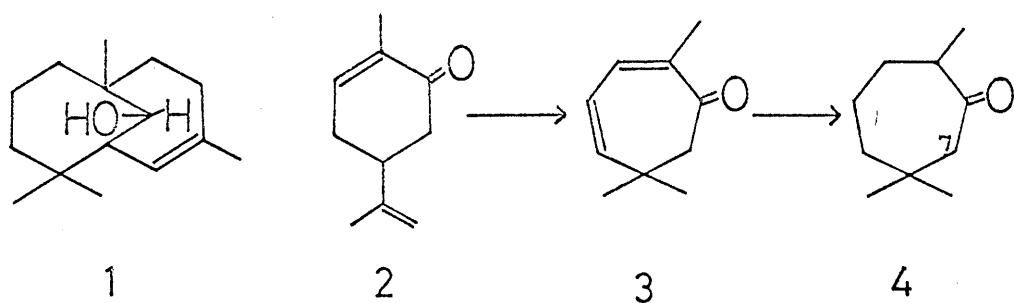
a. broad singlet, centred on broader absorption

b. value of J showed the hydroxyl group to be quasi-equatorial (see discussion)

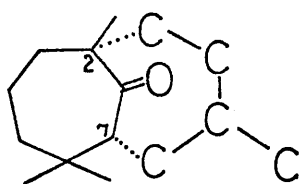
c. signal disappeared on adding D_2O

d. the other signal of the expected doublet was probably obscured by the other methyl resonances

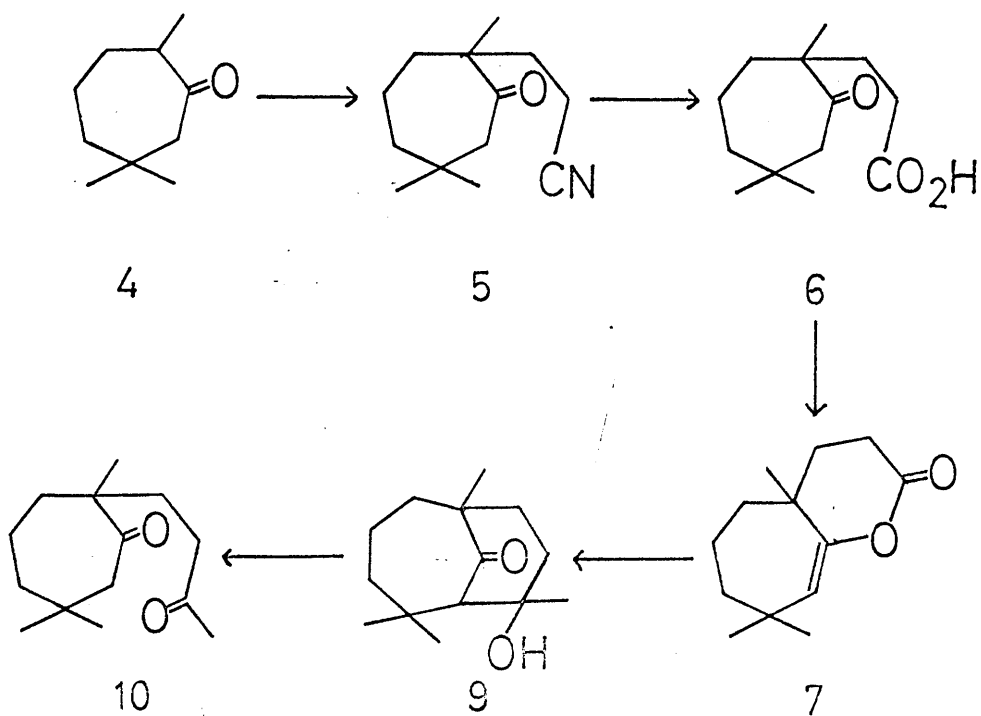
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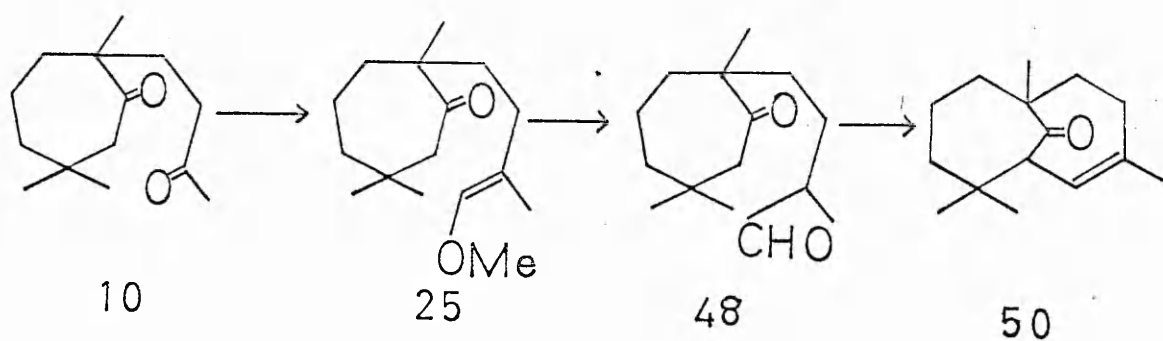
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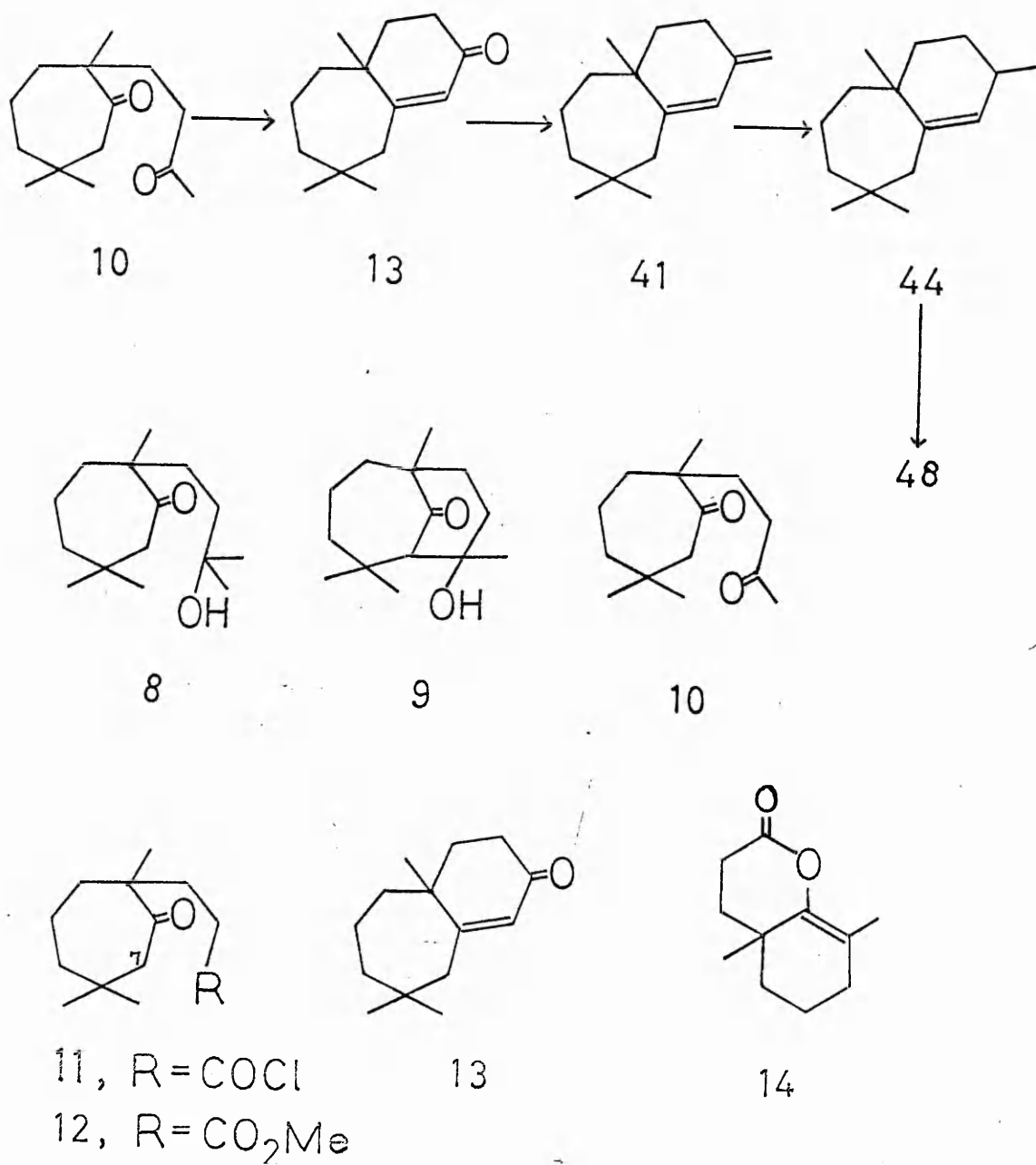
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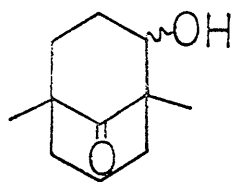


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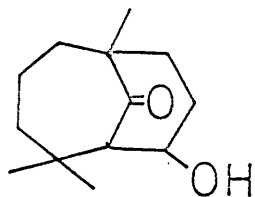


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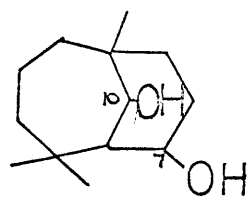




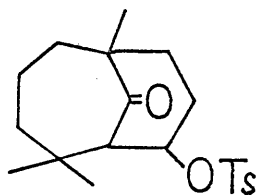
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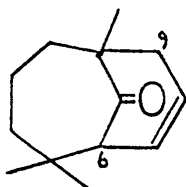
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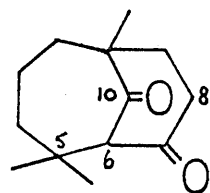
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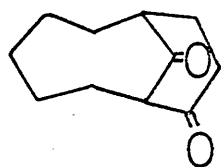
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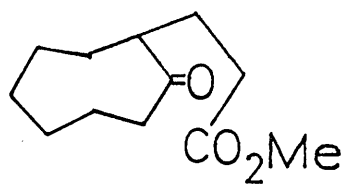
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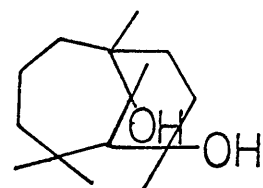
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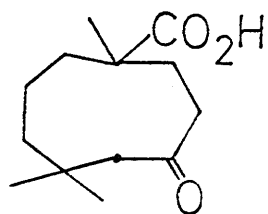
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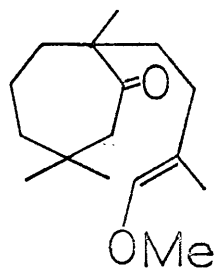
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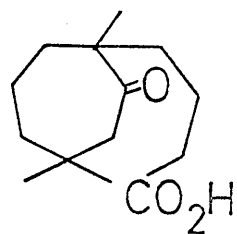
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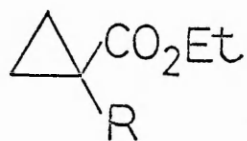
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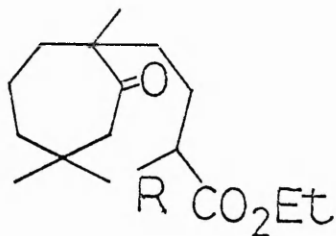
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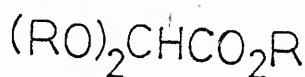
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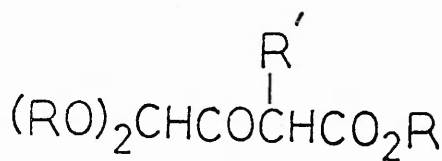
27 $R = \text{CO}_2\text{Et}$
CN



28



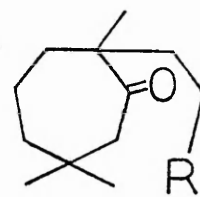
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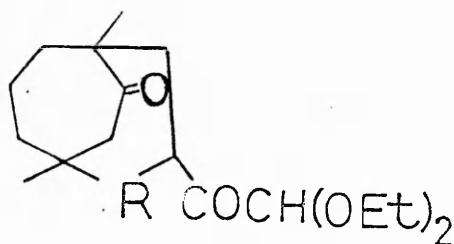
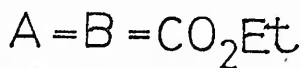
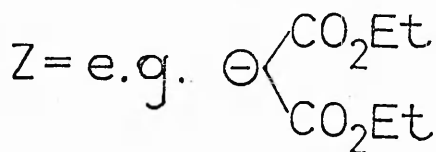
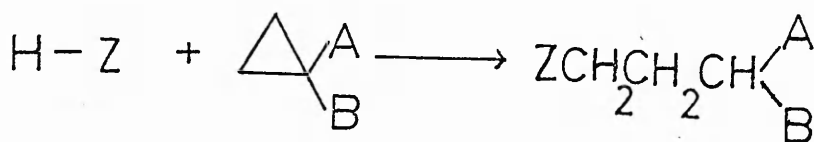


31



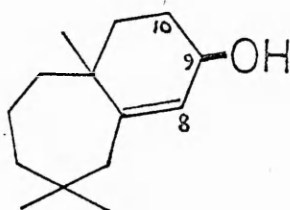
32 $R = \text{CO}_2\text{Et}$

SCHEME F

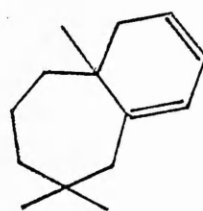


33 $R = \text{CO}_2\text{Et}$

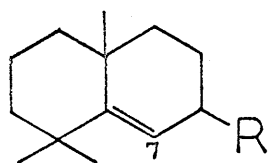
34 $R = \text{H}$



35

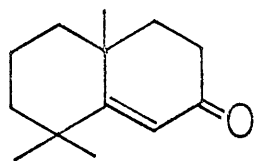


36

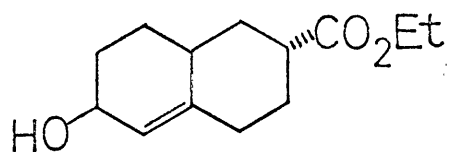


37a, R = β OH

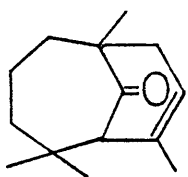
37b, R = α OH



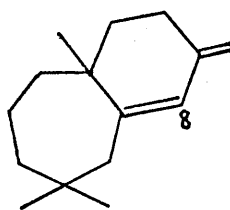
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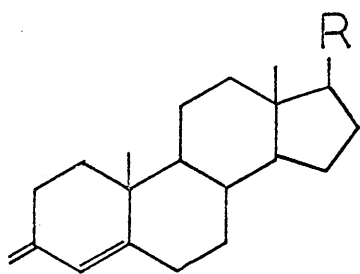
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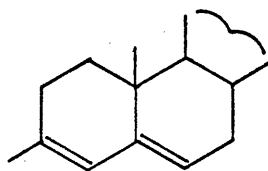
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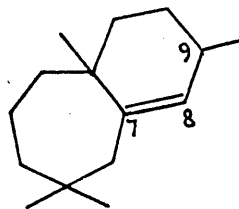
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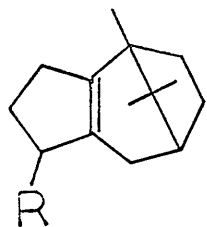
42 R = C_8H_{17}



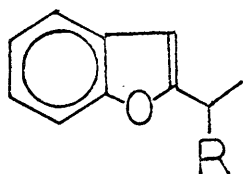
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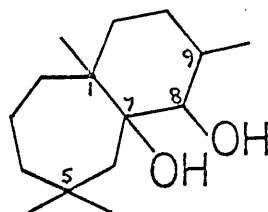
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45

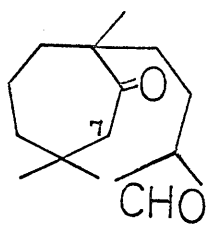


46

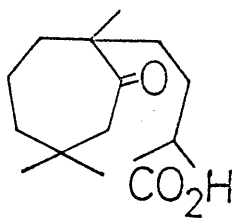


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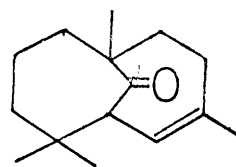
a, R = $=O$, b, R = $=CH_2$, c, R = CH_3



48

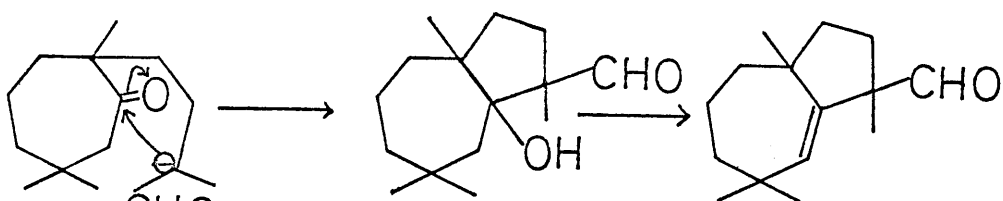


49



50

SCHEME G



48

EXPERIMENTAL

Melting points were determined on a Kofler microscope hot stage and are uncorrected. Boiling points are uncorrected.

Routine infra-red spectra of liquid films and nujol mulls were recorded on Unicam S.P. 200 and S.P. 200G instruments, and solution spectra on a Unicam S.P. 100 double-beam spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum conditions.

Ultra-violet absorption spectra were determined on a Unicam S.P. 800 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R.S.10 (60Mc/s) spectrometer, using solutions in deuteriochloroform with tetramethylsilane as internal reference.

Gas-liquid chromatography was carried out on Pye-Argon and Perkin-Elmer F11 Gas Chromatographs. Mass spectra were recorded on an A.E.I. M.S.9 spectrometer.

Routine and preparative thin layer chromatography (TLC) employed Kieselgel G (Merck) silica, with 20% or 30% ethyl acetate in light petroleum as the solvent system. Chromatoplates were developed with iodine vapour.

All organic extracts were dried over anhydrous magnesium sulphate, and unless otherwise stated, previously washed with brine.

Eucarvone (3)

Eucarvone was prepared from carvone (via carvone hydro-
²⁶bromide) by the method of Wallach ²⁷. Yield 62%, b.p. 44°/0.05mm.,
²⁷ n_D^{27} 1.5050. (Lit. 65% ⁷², b.p. 82-84°/8mm., n_D^{25} 1.5056).

Tetrahydroeucarvone (4)

Hydrogenation of eucarvone by the method of Barnes and
²⁸Houlihan yielded tetrahydroeucarvone. Yield 84%, b.p. 39°/0.4mm.,
²⁶ n_D^{26} 1.4565, semicarbazone m.p. 171-173° (3x aqueous EtOH).
 (Lit. 74%, b.p. 42-43.5°/0.4 mm., n_D^{25} 1.4548, semicarbazone m.p.
 185-187°).
 IR, table 1; NMR, table 6.

2-(β -cyanoethyl)-2,6,6-trimethylcycloheptanone (5)

A solution of tetrahydroeucarvone (30.8 gm.; 0.2M) and
 Triton B (40% aqueous solution; 4 ml.) in ethanol (150 ml.) was warmed
 to 50°, and acrylonitrile ²⁹(21.2gm.; 0.4M) was added dropwise with
 stirring over 1½ hr. After being stirred for 5 hr. at the same
 temperature, the dark yellow mixture was acidified (dilute HCl) and
 extracted with ether. The organic extracts were washed (brine),
 dried, and evaporated, and the residue distilled, yielding unreacted
 tetrahydroeucarvone (8.4gm.), and (5) as a colourless oil which slowly
 solidified (17.2gm.; 57% based on consumed tetrahydroeucarvone),
 b.p. 104°/0.3mm., m.p. 44.5-46.0° (light petroleum 40-60°).
 Found: C, 75.13; H, 10.18; N, 6.75. $C_{13}H_{21}ON$ requires C, 75.32; H,
 10.21; N, 6.76.

Semicarbazone, m.p. 46.0-46.5° (aqueous EtOH).

IR, table 1; NMR, table 6; mass spectrum, table 5.

2-(β -carboxyethyl)-2,6,6-trimethylcycloheptanone (6)

The ketonitrile (5), (16.56 gm.; 0.08M), dissolved in dioxan (200 ml.), was added to concentrated hydrochloric acid (80 ml.) in water (80 ml.), and the mixture stirred under reflux for 3 days. The ether extract was washed with saturated sodium bicarbonate solution. Ether extraction of the acidified bicarbonate layer yielded (6) as a brown oil which usually slowly solidified (17.7 gm.; 98%). The very pale yellow oil, b.p. ca. 125°/0.4 mm., obtained by distillation, solidified, and was recrystallised from pentane as a colourless solid, m.p. 57-58°.

Found: C, 69.40; H, 9.31. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80.

IR, table 1; NMR, table 6; mass spectrum, table 5.

1,5,5-trimethyl-8-oxabicyclo(5.4.0) undec-6-en-9-one (7)

Sodium acetate (500 mg.) was added to a solution of the ketoacid (6), (11.3 gm.; 0.05M), in acetic anhydride (500 ml.) and the mixture refluxed for 4 hr.^{30,25} Excess acetic anhydride was removed by distillation under reduced pressure and the residue dissolved in ether. Distillation of the filtered, evaporated ether solution afforded (7) as a colourless oil, b.p. ca. 130°/0.8 mm., (8.0 gm.; 77%). A sample was redistilled (b.p. 70-80°/0.05mm.), and on standing became a colourless crystalline solid, too soluble to be recrystallised even from the less polar solvents. It also appeared to be hygroscopic, and

satisfactory analysis figures could not be obtained.

IR, table 4; NMR, table 8; mass spectrum, table 5.

Attempted preparations of the 1,5-dione (10)

a) Treatment of the enol lactone (7) with methyl magnesium iodide

i) 0.5 M excess of Grignard reagent added to enol lactone (7)³¹.

A suspension in dry ether (5 ml.) of MeMgI (3.75mM), prepared from magnesium (91 mg.) and methyl iodide (533 mg.) was added dropwise with stirring to a solution of the enol lactone (7) (520 mg.; 2.5mM) in dry ether (25 ml.). After 1 hr. stirring, the mixture was acidified (10% dilute HCl), and extracted with ether. The ethereal layer was washed with saturated sodium bicarbonate solution to separate neutral material (184 mg.) from ketoacid (335 mg.). The former was shown by IR and TLC to be unreacted (7).

ii) enol lactone (7) added to a 5 M excess of Grignard reagent³².

An ethereal solution of (7), (520mg.; 2.5 mM), was added over 1 hr. dropwise with stirring to MeMgI (15mM). After being stirred at reflux for 3 hr., extraction as in (i) yielded acidic material (52 mg.), and a neutral pale yellow oil (445 mg.), which exhibited strong carbonyl (1700 cm.⁻¹) and hydroxyl (3500 cm.⁻¹) absorption in the IR, and contained three compounds, in amounts decreasing with polarities (TLC). Repetition of the reaction without heating to reflux, yielded an identical product (435 mg.). Chromatography of both products on silica (30 gm.), eluting with light petroleum/EtOAc mixtures afforded: the least polar

component (21 mg.; eluted with petrol), which showed weak IR carbonyl absorption; the middle component, (121 mg.; eluted with petrol/ 1 and 2% EtOAc), identical (IR,TLC) to 1,5-dione (10) from the reaction between MVK and (4); and the most polar component, a yellow oil, (587 mg.; eluted with petrol/ 5-10% EtOAc).

Distillation of the last gave a colourless oil, b.p. 90-95°/0.5mm., shown to be 2-(~~8~~-hydroxyisoamyl)-2,6,6-trimethylcycloheptanone (8) from its IR, NMR and mass spectra (tables 1, 6, and 5 respectively).

b) Treatment of the ketonitrile (5) with methyl Grignard reagent

A mixture of the ketonitrile (5), (2.07 gm.; 10 mM), and MeMgBr (20 mM) was refluxed for 2 hr.³³ Extraction as in (a) yielded acidic material (30 mg.) and a neutral yellow oil (1.7 gm.), which contained considerable unchanged (5), (IR, TLC), together with a compound of similar polarity and another much less polar (TLC). This material was not further examined due to the small extent of reaction.

Ketonitrile (5), (1.035 gm.; 5 mM), on treatment with MeMgI³³ (40 mM) formed a neutral product (952 mg.) showing a doublet in the IR carbonyl region at 1720 and 1700 cm.⁻¹. TLC analysis indicated only a trace of starting material, and four or five other less polar components. This complex mixture was not further investigated.

c) Treatment of the ketonitrile (5) with methyl lithium

Following the procedure used in the following experiment, methyllithium (60 mM) and the ketonitrile (5), (1.552 gm.; 7.5 mM), were stirred under reflux for 3 hr.³³ The neutral product (1275 mg.) exhibited strong carbonyl (1710 cm.^{-1}) and weak hydroxyl (3500 cm.^{-1}) absorption in the IR, and consisted of three main compounds (TLC). Separation by preparative TLC (thickness 1 mm., eluant light petroleum/30% EtOAc) yielded from the predominant central band, reasonably pure 1,5-dione (10), (492 mg.; 29%), identical (IR, NMR) with that obtained by condensation of MVK with (4), (vide infra). Later runs however gave lower yields of material containing much less (10), and more of a less polar compound. For example, the product (1.34 gm.) from the ketonitrile (2.58 gm.; 12.5 mM) afforded after chromatography only 0.18 gm. (6.5%) of (10).

d) Treatment of the ketoacid (6) with methyllithium

Methyl iodide (2.84 gm.; 20 mM) was added dropwise over 30 min. to a stirred suspension of lithium (280 mg.; 40 gm. A) in dry ether (10 ml.). The mixture was stirred under reflux for 1 hr., by which time almost all the lithium had dissolved. The colourless cloudy solution was filtered through glass wool into a pressure-equilibrated dropping funnel and added over 5 min. to a stirred solution of the ketoacid (6), (1.13 gm.; 5 mM), in dry ether (15 ml.).³⁴ (N_2 atmosphere throughout). After being heated at reflux for 2 hr., water was added carefully to the cooled solution. The ether extract was washed with saturated sodium bicarbonate solution to separate unchanged acid (1046 mg.)

from neutral material (50 mg.), shown by TLC to be a mixture of three compounds. Further attempts at this reaction gave similar results. Owing to the low yield, and complexity of the product, the material was not further examined.

e) Attempted preparation of pure ketoacidchloride (11)

a) thionyl chloride.

The ketoacid (6), (11.3 gm.; 0.05 M), and thionyl chloride (12.1 gm.; ca. 20 ml.; 0.1 M) were heated to reflux for 3 hr. Excess thionyl chloride was distilled under reduced pressure (water pump). Distillation afforded a pale red viscous oil which partially solidified (7.7 gm.), b.p. 120-122°/0.15 mm. The distillate contained the title compound (odour; IR 1700, 1800 cm^{-1}), but the predominant component was the enol lactone (7), (IR 1760, 1660 cm^{-1}). TLC also indicated the presence of two compounds, the less polar being (7).

b) Oxalyl chloride (5ml.; 0.06 M) was added to a solution of the ketoacid (6), (2.26 gm.; 0.01 M), in dry benzene (20 ml.). The mixture was stirred for 8 hr., and left overnight. Benzene and excess oxalyl chloride were distilled under reduced pressure (water pump). The residue was shown by IR and TLC to be a mixture similar to that obtained in (a).

2-(~~B~~-carboethoxyethyl)-2,6,6-trimethylcycloheptanone (12)

The ketoacid (6), (2.26 gm.; 0.01 M), dissolved in dry Et_2O

(20 ml.), was treated dropwise with ethereal diazomethane until a yellow colour persisted. The solution was left overnight, filtered to remove polymer, and evaporated, yielding (12) as a pale yellow oil (2.24 gm.; 93%). Distillation afforded a colourless oil, b.p. 106-107°/3mm.

Found: C, 69.21; H, 9.40. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.07.

IR, table 1; NMR, table 6; mass spectrum, table 5.

f) Treatment of the ketoester (12) with dimethylsodium

A 50% mineral oil dispersion of sodium hydride (1.2 gm.; ca. 25 mM) was washed thoroughly with light petroleum 40-60°, and the washings decanted. The flask was then filled with nitrogen, and dimethylsulphoxide (DMSO), (25 ml.; distilled from calcium hydride) was added dropwise with stirring. After heating the mixture at 70-75° for 1 hr., and cooling, there was obtained a pale grey solution of the sodium salt of DMSO.³⁶ To 15 ml. of this solution (ca. 15 mM) was added dry THF (15 ml.), and, with cooling in an ice bath, the ketoester (12), (2 gm.; 8.3 mM), dropwise over several minutes. After being stirred for 30 min. at room temperature, the solution was poured into water (90 ml.), acidified to pH 3-4 (dilute HCl), and extracted with chloroform. The organic extract was washed (3 x water), dried, and evaporated, leaving a yellow oil (2.36 gm.). The large amount of acid present (1.8 gm.) was removed by washing with saturated sodium bicarbonate solution, leaving neutral material (473 mg.). This consisted of two compounds, both less polar

than the ketoester (12). Since the material showed no carbonyl absorption in the IR, it was not further examined.

2-(3'-ketobutyl)-2,6,6-trimethylcycloheptanone (10)

Treatment of tetrahydroeucarvone (19.86 gm.; 129 mM) in dry ether (100 ml.) with potassium hydroxide (0.84 gm.; 15 mM) in dry ethanol (15 ml.) and methyl vinyl ketone (4.90 gm.; 70 mM) by a method³⁷ similar to that for the preparation of (13) (*vide infra*), yielded on distillation unchanged (4), (10.01 gm.), and a fraction (7.40 gm.) with b.p. 120-124°/0.8 mm. This material contained mainly (10), with small amounts of (4) and (13), and was chromatographed on silica (370 gm.). Tetrahydroeucarvone (0.3 gm.) was eluted by light petroleum/5-50% benzene, the enone (13), (0.82 gm.), by benzene, and (10), (5.48 gm.; 39.5% based on consumed (4)), by benzene/10-50% chloroform. The dione (10) was obtained as a colourless oil by distillation, b.p. 117-120°/0.3 mm.

IR, table 1; NMR, table 6; mass spectrum, table 5.

The mono-2,4-dinitrophenylhydrazone was crystallised from ethanol as a yellow crystalline solid, m.p. 113-114°.

Found: C, 59.58; H, 6.92; N, 13.95. C₂₀H₂₈N₄O₅ requires C, 59.39; H, 6.98; N, 13.85 $\nu_{\text{C=O}}$: 1699 cm.⁻¹

1,5,5-trimethylbicyclo (4.3.1) decan-7-ol-10-one (16)

A suspension of lithium aluminium hydride (2.56 gm.; 67 mM) in dry THF (100 ml.) was added dropwise to a stirred solution of

t-butanol (14.94 gm.; 201 mM). This suspension of lithium aluminium tri-(t-butoxy) hydride³⁸ was added dropwise over 1.5 hr. in a nitrogen atmosphere to a stirred solution of the enol lactone (7), (10.0 gm.; 48 mM), in THF (100 ml.) at -70° (acetone-dry ice bath).²⁵ The mixture was allowed to warm to room temperature while being stirred overnight. After addition of brine, acidification (dilute HCl), and ether extraction, the ether layer was washed with saturated sodium bicarbonate solution, brine, and dried and evaporated, leaving a pale yellow oil (7.30 gm.). Ether extraction of the acidified bicarbonate layer afforded ketoacid (6), (2.39 gm.). The neutrals consisted of three compounds, the most polar being (16), and the next most polar, which varied in amounts in different runs, probably being unchanged (7) (similar R_f). Chromatography on silica (360 gm.), eluting with light petroleum/EtOAc mixtures, afforded (16) as a pale yellow oil (3.9 gm.; 39%), eluted with light petroleum/20-30% EtOAc. Distillation furnished axial (16) as a colourless oil, b.p. 80-90°/0.1 mm., which slowly solidified to a colourless crystalline solid, m.p. 71-76°. Later runs afforded axial-equatorial mixtures which became colourless liquid-solid mixtures on distillation, final m.p. ca. 70°.

IR, table 2; NMR, table 7, mass spectrum, table 5.

1,5,5-trimethylbicyclo (4.3.1) decan-7,10-diol (17)

A solution of the ketol (16), (210 mg.; 1 mM), in dry THF (7 ml.) was stirred 24 hr. under reflux with lithium aluminiumhydride

(114 mg.; 2 M excess). Acidification (dilute HCl) and ether extraction gave a viscous pale yellow oil, consisting of diol (17), unchanged (16),* and traces of a less polar compound. Separation by preparative TLC (thickness 0.8 mm., eluant: light petroleum/60% EtOAc) afforded pure diol (62 mg.; 29%), m.p. 91-97° (petrol 60-80°). Found: C, 73.45; H, 11.50. $C_{15}H_{24}O_2$ requires C, 73.54; H, 11.39. IR, table 2; NMR, table 7; mass spectrum, table 5.

* The products from reductions carried out under several different conditions always contained unchanged (16). After a 45 hr. reflux with excess lithium aluminium tri-(t-butoxy) hydride, the product contained only a trace of (16), and also several less polar compounds in small concentrations.

1,5,5-trimethyl-7-tosyloxy-bicyclo(4.3.1) decan-10-one (18)

To the ketol (16), (420 mg.; 2 mM), dissolved in dry pyridine (2 ml.), was added a solution of tosyl chloride (400 mg.; slight excess of 2 mM) in dry pyridine (2 ml.). After being left at room temperature for 14 days (the product after 4 days contained an appreciable amount of unreacted (16)), brine was added, the mixture acidified (dilute HCl) and extracted with ether. The ether extract was washed (brine), dried, and evaporated, leaving (18) as a yellow oil which slowly solidified (437 mg.; 60%). A colourless crystalline solid, m.p. 114-115°, was obtained by recrystallisation from ethanol. Found: C, 66.12; H, 7.58. $C_{20}H_{28}O_4S$ requires C, 65.91; H, 7.74.

IR, table 2; NMR, table 7; mass spectrum, table 5.

1,5,5-trimethylbicyclo (4.3.1) dec-7-en-10-one (19)

a) from ketotosylate (18)

The ketotosylate (18), (91 mg.; 0.25 mM), was added in small portions over 5 min. to a stirred solution of sodium (7 mg.) in dry ethanol (2 ml.). The mixture was stirred under reflux for 2 hr., cooled, neutralised with acetic acid, diluted with water and extracted with light petroleum 60-80° (3X).⁴⁰ Ether extraction of the aqueous layer afforded unchanged (18), (5 mg.). The petrol extract was washed with saturated sodium bicarbonate solution, brine, and dried. Evaporation of solvent under reduced pressure yielded (19) as a volatile colourless oil with a camphoraceous odour (33 mg.; 73% based on consumed 8) $UV \lambda_{Max}^{EtOH} 206 m\mu$ ($\epsilon 3600$). IR, table 2; NMR, table 7; mass spectrum, table 5.

b) attempted preparation from ketol (16)

A solution of the ketol (16), (105 mg.; 0.5 mM), in dry benzene (2 ml.) was refluxed on the steam bath for 2 hr. with excess poly-phosphoric acid (treatment at room temperature caused incomplete reaction). Addition to ice, followed by ether extraction, afforded a volatile yellow oil (75 mg.), containing a rather non-polar compound (large R_f in hexane), and several more polar components (TLC). Routine IR showed carbonyl absorption at 1705 cm^{-1} . Chromatography on silica (eluant: pentane) afforded the predominant component as a

colourless volatile oil (18 mg.), exhibiting no carbonyl absorption in the IR.

1,5,5-trimethylbicyclo (4.3.1) decan-7,10-dione (20)

A solution of ketol (16), (2.10 gm.; 0.01 M), in acetone (50 ml.) was treated for 30 min. with excess Jones reagent⁴² at 0°. Methanol was added to destroy excess oxidant. After addition of brine, extraction with ethyl acetate furnished (20) as a colourless oil (1.89 gm.; 91%), b.p. 60-70°/0.02mm.

IR, table 2; NMR, table 7; mass spectrum, table 5.

GLC column: 1% PEGA. Temp. : 125°. F.R. 48 ml./min. R.T. : 5 min.

Mono-2,4-dinitrophenylhydrazone, m.p. 188-191° (EtOH).

Found: C, 58.80 ; H, 7.03. $C_{19}H_{24}N_4O_5$ requires C, 58.75; H, 6.23.

Attempted cyclisation of ketoacid (6) to dione (20)

Tetralin (5ml.) and p-toluene sulphonic acid (100 mg.) were heated together to reflux for 1 hr. in a Dean and Stark water separator.⁴⁴ The ketoacid (6), (113 mg.; 0.5 mM), was added, and the mixture was refluxed for 2 hr. Brine was added, and the ether extract was washed with saturated sodium bicarbonate solution and brine, and dried. The neutral product (111 mg.), a brown oil, had IR absorption at 1680 cm^{-1} (C=O), and exhibited marked streaking in TLC. After distillation however, TLC showed it to be a mixture of four compounds. The most polar of these had an R_f value similar to that of (20), but the

mixture was not further investigated.

Attempted cyclisation of the ketoester (12) to the dione (20)

The procedure was based on a reaction by Marshall and Scanio.⁴⁵

A 51% dispersion of sodium hydride in mineral oil (0.6 gm.) was washed with dry benzene and dry 1,2-dimethoxyethane (DME) and added to a solution of the ketoester (12), (780 mg.; 3.25 mM), in DME (10 ml.). After 14 hr. reflux, acetic acid (1.5 ml.) and dry ether (10 ml.) were added carefully to the cooled solution. The ether extract was washed with saturated sodium bicarbonate solution to separate neutral material (72 mg.) from ketoacid (6), (571 mg.). The former contained some unchanged ester, but none of the desired dione.

Treatment of the dione (20) with methyl magnesium iodide (MeMgI)

A solution of the dione (20), (104 mg.; 0.5 mM), in dry ether (3 ml.) was added dropwise with stirring to an ethereal suspension of MeMgI (0.65 mM). After being refluxed for 1 hr., water was carefully added. Ether extraction yielded a pale yellow oil (99 mg.), containing mostly unchanged (20), and two more polar compounds,

probably the C₇ epimeric ketols (9), (TLC). Repetition of this procedure with a larger excess of MeMgI (2.5 mM) gave a product (95 mg.) containing in addition to the above, a highly polar compound, probably the diol (22). The products were combined and stirred under reflux for 16 hr. with MeMgI (2.5 mM), affording material (174 mg.) of largely unchanged composition (TLC). Chromatography on silica (9 gm.) using light petroleum/EtOAc mixtures, afforded unreacted dione (20), (48 mg.; eluant petrol/1 and 2% EtOAc), a mixture of two compounds, probably the epimeric ketols (9) (66 mg.; eluant petrol /5-10% EtOAc), and the diol (22), (40 mg.; eluant petrol/20-30% EtOAc), which after distillation (b.p. 85-95°/0.1 mm.) and re-crystallisation from light petroleum 60-80° became a colourless crystalline solid, m.p. 85-114°.

IR, table 2; NMR, table 7.

Conversion of the dione (20) to the ketoacid (6)

A solution of the dione (20), (52 mg.; 0.25 mM), in methanol (5 ml.) was heated to reflux on the steam bath for 30 min. with excess methanolic potassium hydroxide. Methanol was then allowed to evaporate from the straw-coloured solution, and the residue was acidified (dilute HCl). The ether extract was washed with brine, and saturated sodium bicarbonate solution. Ether extraction of the acidified bicarbonate layer gave an acidic yellow oil (54 mg.; 96%). The distilled product was identical (IR, NMR, TLC) to the ketoacid (6).

Sodium borohydride reduction of the dione (20)

The dione (20), (52 mg.; 0.25 mM), dissolved in methanol (3 ml.) was treated with sodium borohydride (10.5 mg.; 0.275 mM), and the mixture was stirred overnight. Water was added, and ether extraction yielded a pale yellow oil (50 mg.; 95%) which consisted of two components (TLC). GLC Column: 1%. PEGA Temp: 125°. F.R. 40 ml./min. R.T. 16.0 min. (identical R.T. to axial (16) from reduction of enol lactone (7)) and 37.6 min. (hence equatorial ketol (16)). The composition of the mixture (by integration of the peaks) was 1:1.

Treatment of the dione (20) with diazoethane

a) N-nitroso-N-ethylurethan method^{47,48}

Anhydrous sodium carbonate (3 mg.) was added to a solution of the dione (20), (104 mg.; 0.5 mM), in ethanol (1 ml.) and ether (1 ml.). N-nitroso-N-ethylurethan (ca. 235 mg.; 2 mM; prepared from⁷³ N-ethyl carbamate⁷⁴) was added dropwise over 5 min., and the mixture stirred for 30 hr. After acidification (dilute H₂SO₄), and 26 hr. stirring, brine was added, and the solution extracted with ether. The ether extract was washed (brine), dried, and evaporated. Distillation of the residue gave a colourless oil (73 mg.), b.p. 65-75°/0.1 mm., which consisted solely of unchanged (20), (IR, TLC, NMR and GLC).

b) N-nitroso-N-ethylurea method

Excess N-nitroso-N-ethylurea was added to a mixture of 40%

aqueous potassium hydroxide (7 ml.) and ether (7 ml.) The resultant yellow organic layer was separated and left for 3 hr. over solid KOH with cooling. It was then added dropwise with stirring to a solution of the dione (20), (52 mg.; 0.25 mM), in dry ether (2 ml.). After being stirred for $2\frac{1}{2}$ hr., the ether solution was washed (brine), dried, and evaporated, affording a pale yellow oil (52 mg.). IR, TLC and GLC showed it to contain only (20).

Treatment of the dione (20) with diazomethane⁴⁷

The dione (20), (31 mg.; 0.15 mM), dissolved in dry ether (1 ml.) was treated with excess ethereal diazomethane. After being stirred for 21 hr., the solution was evaporated, yielding a pale yellow oil (30 mg.) consisting only of starting dione (IR, TLC, GLC).

Treatment of the dione (10) with triphenylphosphinemethoxymethylene

The method used was that for the preparation of methoxymethylenecyclohexane.⁷⁵

A suspension in dry ether of phenyllithium⁷⁶ (5 mM)- prepared from bromobenzene (0.78 gm.) and lithium (70 mg.) - was added dropwise with stirring in a nitrogen atmosphere to a suspension of triphenyl methoxymethylphosphonium chloride (1.70 gm.; 5 mM) in dry ether (15 ml.). The resultant cloudy red solution, consisting of a suspension of methoxymethylenetriphenylphosphorane,⁵⁰ was stirred for 10 min., cooled to -70° (dry ice- acetone bath) and the dione (10),

(896 mg.; 4 mM), in ether (2 ml.) was added dropwise. The mixture was stirred for 15 min. at -70° , and 19 hr. at room temperature. The cloudy off-white solution was filtered, the filtrate evaporated, and the residue dissolved in acetone, diluted with a large volume of light petroleum $40-60^{\circ}$, and carefully filtered. Repetition of this process removed most of the triphenylphosphine oxide, and yielded a yellow oil (ca. 1 gm.), which was freed from starting dione (10) by distillation. The residue (220 mg.) consisted of a trace of unchanged (10), Ph_3PO , a compound slightly less polar than (10), and another highly polar (remaining on baseline in TLC). Removal of Ph_3PO by chromatography left a brown oil, IR examination of which did not detect the presence of the desired enol ether.

Similar products were obtained by adding the dione at room temperature, or heating the mixture to reflux for 2 hr.

Attempted preparation of 1,1-dicarbethoxycyclopropane (27, R=CO₂Et)

The method of Doxand Yoder⁵³ afforded on distillation in the range $200-220^{\circ}$ a colourless oil. (Lit. title compound b.p. $214-216^{\circ}/748$ mm.; 40%). Both its IR and NMR spectra showed it to be unchanged diethyl malonate (b.p. 199°). In particular, the NMR spectrum showed no signal due to cyclopropyl protons.

Attempted preparation of 1-carbethoxy-1-cyano-cyclopropane (27, R=CN)

The method of Perkin,⁵⁴ modified by Jones and Scott,⁵⁴

yielded from ethylcyanoacetate (100 gm.; b.p. 206°) after steam distillation a colourless oil (13.5 gm.). Fractional distillation (Lit. title compound, b.p. 212-216°; 64.4 gm.; 76%) afforded one main fraction; b.p. 206-210°, shown by its IR and NMR spectra to be unreacted ethylcyanoacetate.

2-(β -carbethoxyethyl)-2,6,6-trimethylcycloheptanone (32)

A mixture of ketoacid (6), (6.78 gm.; 0.03M), ethanol (100 ml.) and dilute sulphuric acid (60 ml.) were stirred for 1 hr. After addition of brine, the ether extract was washed with saturated sodium bicarbonate solution, (ether extraction of the acidified bicarbonate layer affording unchanged (6), (1.6 gm.)), brine, dried and evaporated, yielding (32) as a pale yellow oil (5.6 gm.; 88% based on consumed 4). Distillation gave a colourless oil, b.p. 96°/0.08 mm.

IR, table 1; NMR, table 6; mass spectrum, table 5.

Attempted condensation of ketoester (32) and ethyl diethoxyacetate

The forcing conditions described for condensations with
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ethyl dimethoxyacetate were employed.

A mixture of the ketoester (32), (2.54 gm.; 10 mM), and ethyl diethoxyacetate (29, R=Et), (1.76 gm.; 10 mM) in dry benzene (10 ml.) was added to a suspension of sodium ethoxide (from 240 mg. sodium and 7.5 ml. dry ethanol, followed by evaporation of solvent)

in dry benzene (10 ml.). The benzene-ethanol azeotrope was removed over 5 hr. from the refluxing, stirred solution via a fractionation column. Cold dilute acetic acid (5 ml.) in water (5 ml.) was added to the cooled mixture. The ether extract was washed with saturated sodium bicarbonate solution, saturated sodium hydroxide solution, and brine, and dried. Removal of solvent left a yellow oil (1.3 gm.) consisting of unchanged (32), (IR, TLC). Ether extraction of the acidified bicarbonate and hydroxide extracts gave in each case acidic material (IR, TLC; 0.6 gm. in all).

1,5,5-trimethylbicyclo(5.4.0) undec-7-en-9-one (13)

a) from tetrahydroeucarvone.

Potassium hydroxide (455 mg.; 8.12 mM) in dry ethanol (5 ml.) was added to tetrahydroeucarvone (16.69 gm.; 108.3 mM) in dry ether (100 ml.). The mixture was cooled to 0°, and freshly-distilled methyl vinyl ketone ³⁷ (3.79 gm.; 54.15 mM) in ether (25 ml.) was added over 1 hr. dropwise with stirring. The ice-bath was removed, and after being stirred for 1 hr., the pale red solution was poured on to ice, neutralised (concentrated HCl), and extracted with ether. The product, a dark yellow oil (ca. 19.5 gm., comprising tetrahydroeucarvone, 1,5-dione, and (13)) was dissolved in methanol (100 ml.) and refluxed overnight with potassium hydroxide (5 gm.) in methanol (50 ml.). Ether extraction (assisted by the addition of brine), removal of solvent, and distillation afforded tetrahydroeucarvone

(9.87 gm.), b.p. ca. $35^{\circ}/0.15$ mm., and (13), (5.96 gm.; 65% based on consumed tetrahydroeucarvone) as a pale yellow oil which slowly solidified, b.p. $92-94^{\circ}/0.15$ mm. Recrystallisation and cold filtration from pentane furnished with difficulty a colourless crystalline solid, m.p. $67.5-68.5^{\circ}$ $UV\lambda_{\text{Max}}^{\text{EtOH}}$ 245 m μ (ϵ 1500.)

The 2,4-dinitrophenylhydrazone was crystallised from ethylacetate as red needles, m.p. $210-213^{\circ}$.

Found: C, 62.27; H, 6.79; N, 14.58. $C_{20}H_{26}N_4O_4$ requires C, 62.16; H, 6.78; N, 14.50.

IR, table 4; NMR, table 8; mass spectrum, table 5.

b) from 2-(3'-ketobutyl)-2,6,6-trimethylcycloheptanone (10)

Potassium hydroxide (260 mg.) in methanol (3 ml.) was added to a solution of the 1,5-dione (10), (224 mg.; 1 mM), in methanol (2 ml.), and the mixture refluxed for 4 hr. on the steam bath. Brine was added, and the ether extract was washed (brine), dried and evaporated, yielding (13) as a pale yellow oil (198 mg.; 96%) identical to that from (a), (IR, TLC).

1,5,5-trimethylbicyclo(5.4.0)undec-7-en-9 β -ol (35)

A solution of the enone (13), (206 mg.; 1 mM), in ethanol (15 ml.) was treated with sodium borohydride (38 mg.; 1 mM), and refluxed 13 hr. with stirring. Water was added to the cooled solution, and the ether extract was washed (brine), dried and evaporated to yield (35) as a pale yellow crystalline solid (208 mg.; 100%). This

material was soluble in pentane at room temperature, but colourless (35) obtained by distillation was recrystallised and filtered cold from that solvent, affording colourless needles, m.p. 83-85°. Some diene (formed by dehydration) was present in the distilled sample (TLC), and was removed by preparative TLC (eluant: light petroleum 40-60°).

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From its NMR spectrum (table 8) the hydroxyl group was seen to be quasi-equatorial (β).^{57,58}

IR, table 4; mass spectrum, table 5.

1,5,5-trimethylbicyclo(5.4.0)undeca-7,9-diene (36)

The unsaturated alcohol (35), (208 mg.; 1mM), dissolved in dry benzene (3 ml.) was stirred for 1½ hr. with excess polyphosphoric acid. Addition to ice, followed by ether extraction, yielded (36) as a colourless oil (178 mg.; 94%). $\lambda_{\text{Max}}^{\text{EtOH}}$ 273 m μ (ϵ 10300) IR, table 4; mass spectrum, table 5.

Attempted cyclisation of the dione (10) to 1,5,57-tetramethylbicyclo(4.3.1) dec-7-en-10-one (40)

a) refluxing with p-toluenesulphonic acid (PTSA) in benzene⁶⁰

A solution of PTSA (500 mg.) in dry benzene (15 ml.) was heated at reflux for 2 hr. in a Dean and Stark water separator. The dione (10), (448 mg.; 2mM), dissolved in dry benzene (3 ml.) was added

to the cooled solution, and the mixture refluxed a further $2\frac{1}{2}$ hr. After neutralisation with solid potassium carbonate, the solution was left overnight, and filtered. The filtered solid was washed with benzene, and the combined benzene extracts were washed, dried, and evaporated, yielding a brown oil (434 mg.). The product contained mainly unreacted dione and the enone (13) (IR, TLC), and a very small amount of a less polar compound (TLC). Chromatography on silica using petrol 40-60°/ benzene 2/1 as eluant furnished 6 mg. of the latter component, which had no carbonyl absorption in the IR spectrum, and hence was not the desired compound.

b) refluxing with PTSA in toluene

A solution of PTSA (500 mg.) in toluene (10 ml.) was refluxed for 5 hr. in a water separator. After addition of the dione (10), (112 mg.; 0.5 mM), in toluene (1 ml.), followed by a 5 hr. reflux, the extraction procedure used in (a) yielded a brown oil (112 mg.). The product contained only the enone (13), (IR, TLC), and a small amount of a less polar component (TLC), the latter probably causing a band at 1740 cm^{-1} in the IR. Chromatography on silica using light petroleum 40-60°/ benzene mixtures gave a fraction (8 mg.) with no carbonyl absorption in the IR, and a fraction (5 mg.) with IR absorption at 1740 cm^{-1} , which, because of lack of material, was not further investigated. Elution with benzene, and benzene/chloroform, yielded reasonably pure enone (13), (83mg.).

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c) concentrated sulphuric acid

Concentrated sulphuric acid (1 ml.) was added dropwise to the dione (10), (448 mg.; 2 mM), and the mixture stirred for 72 hr. in a stoppered flask. Careful addition of saturated sodium bicarbonate solution and ether extraction furnished a yellow oil (386 mg.), containing mainly unchanged (10) and a little of the enone (13), (IR, TLC), and, as in (a) and (b), a trace of a less polar component.

d) Boron trifluoride etherate

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The method used was based on that of Corey and Nozoe.

A mixture of boron trifluoride etherate (3 ml.), dione (10), (224 mg.; 1 mM), and methylene chloride (6 ml.) was heated at reflux for $4\frac{1}{2}$ hr., and then allowed to cool. Addition to water, and ether extraction, yielded a yellow oil (216 mg.) containing approximately equal amounts of unchanged (10) and the enone (13), (IR, TLC).

Only the enone (13), (207 mg.), was present when this material was refluxed for 9 hr. in benzene (6 ml.) with boron trifluoride etherate (3 ml.).

1,5,5-trimethyl-9-methylenebicyclo (5.4.0)undec-7-ene (41)

To a suspension in dry ether of phenyllithium⁷⁶ (20 mM) - prepared from bromobenzene (3.12 gm.) and lithium (278 mg.) - was added dropwise over 5 min. with stirring in a nitrogen atmosphere a suspension of triphenylmethylphosphonium bromide⁶³ (7.14 gm.; 20 mM)

in dry ether (40 ml.). The resultant cloudy yellow mixture, containing a suspension of the Wittig reagent, methylenetriphenylphosphorane, was stirred under nitrogen for 3 hr. A solution of the enone (13), (2.06 gm.; 10 mM) in ether (30 ml.) was added dropwise under nitrogen, destroying the yellow colour, and rendering the solution much cloudier. The mixture was stirred overnight under reflux (without nitrogen), allowed to cool, filtered to remove most of the finely-divided solid, and evaporated under reduced pressure. The yellow oily solid residue was extracted thoroughly with hot light petroleum 40-60°. The petrol extracts were filtered under suction several times to remove colourless triphenylphosphine oxide (Ph_3PO), washed with water(3x), dried and evaporated. The residual yellow oil consisted mainly of (41), with a small amount of Ph_3PO , and a trace of unchanged (13), (TLC). The products from most runs were chromatographed on silica (eluant: light petroleum 40-60°), giving good separation of (41) from its closest chromatographic contaminant, Ph_3PO . However, on one occasion, total rearrangement of (41) occurred, and later runs were purified on neutral alumina grade 3, which gave a less satisfactory but adequate separation. The diene (41) was eluted first as a colourless volatile oil (1.402 gm.; 69%), which underwent very gradual atmospheric oxidation to the enone (13). Despite repeated distillation, satisfactory analysis figures were not obtained. $\lambda_{\text{Max}}^{\text{EtOH}}$ 243 mμ (ε 17800)

IR, table 4; NMR, table 8; mass spectrum, table 5.

1,5,5,9-tetramethylbicyclo(5.4.0)undec-7-ene (44)

The diene (41), (3.23 gm.; 15.83 mM) dissolved in analar ethyl acetate (15 ml.) was hydrogenated in the presence of 5% Pd on charcoal (1.5 gm.). Uptake ceased after about 45 min. Filtration and evaporation of solvent (with minimal heating) under reduced pressure furnished (44) as a colourless, volatile oil (3.00 gm.; 93%).

IR, table 4; NMR, table 8; mass spectrum, table 5.

Attempted ozonolysis of olefin (44)

10% ozone in oxygen was passed for 15 min. through a solution of the olefin (44), (43 mg.; 0.21 mM), in ethyl acetate (5 ml.) at -70° (acetone-dry ice bath). Glacial acetic acid (2 ml.) and zinc powder (60 mg.) were then added. After being stirred at room temperature for 1 hr., the mixture was filtered, and the solvents evaporated. The residue was dissolved in ethyl acetate, and washed with saturated sodium bicarbonate solution, to separate acidic material (6 mg.) from neutral material (29 mg.). The latter showed IR absorption at 1700 cm.^{-1} (C=O), but none at $2650\text{--}2880\text{ cm.}^{-1}$ (C-H str. aldehyde), and consisted of a mixture of several components (TLC). The NMR spectrum showed no aldehydic proton signal.

1,5,5,9-tetramethylbicyclo (5.4.0)undecan-7,8-diol (47)

The hydroxylation procedure used was that of Baran.⁶⁷

Osmium tetroxide (3.5 gm.; 13.79 mM) was added portionwise to a solution of the olefin (44), (2.8 gm.; 13.60 mM), in dry pyridine (50 ml.). After 3 days, the dark brown solution was stirred for 1 hr. with a solution of sodium bisulphite (6.3 gm.) in water (105 ml.) and pyridine (70 ml.). The mixture was extracted with chloroform (5X), and the organic extracts were washed, dried, and evaporated, with the addition of dry benzene to effect azeotropic removal of pyridine. The residual diol (47) was a viscous brown oil (3.05 gm.; 93.5%) which on distillation was obtained as a colourless crystalline solid, which slowly solidified, m.p. 86.5-88.5°.

Found (mass anal.) 240.20752; $C_{15}H_{28}O_2$ requires 240.20892
IR, table 4; NMR, table 8; mass spectrum, table 5.

2-(8-formylbutyl)-2,6,6-trimethylcycloheptanone (48)

a) Attempted cleavage of the diol (47) by sodium metaperiodate

The diol in dry or aqueous methanol was stirred at room temperature under nitrogen with excess sodium metaperiodate⁶⁸ for periods up to 35 hr., but in all cases the diol was recovered unchanged.

b) Cleavage of the diol (47) by lead tetraacetate

Pure diol (47), (102 mg.; 0.425 mM) in dry benzene (3 ml.)

was stirred for 4 hr. with lead tetraacetate⁶⁹ (150 mg.). The mixture was filtered under suction, the filtered solid washed with benzene, and the filtrate washed with water, saturated sodium bicarbonate solution, and brine. Evaporation of the dried benzene layer afforded a neutral pale yellow oil (95 mg.) consisting mainly of (48), with a small amount of a more polar compound (TLC).

IR, table 1 ; NMR, table 6.

Attempted preparation of 1,5,5,8-tetramethylbicyclo(4.4.1)undec-7-en-11-one (50)

a) treatment of ketoaldehyde (48) with base

A solution of the ketoaldehyde (48), (25 mg.), in methanol (3 ml.) was heated for 15 min. on the steam bath with methanolic potassium hydroxide. Addition of brine, and ether extraction afforded a small acidic fraction, and neutral material which contained at least four components (TLC). This complex mixture was not further examined.

b) p-toluenesulphonic acid in refluxing benzene on ketoaldehyde (48)

A mixture of PTSA (70 mg.) in benzene (4 ml.) was heated for two hr. in a water separator. The ketoaldehyde (48), (65 mg.), dissolved in benzene (4 ml.) was then added. The deep red solution obtained after $4\frac{1}{2}$ hr. reflux was cooled, neutralised with excess solid potassium carbonate, and left overnight. The benzene solution obtained on filtration was washed (2 X saturated NaHCO_3 , then 2 X brine) dried, and evaporated. The residual yellow oil contained unchanged (48) and three much less polar compounds. The routine IR spectrum was

similar to that of (48), with a weak additional shoulder at 1670 cm.^{-1}

c) treatment of ketoaldehyde (48) with concentrated sulphuric acid^{17,71}

The ketoaldehyde (48), (25 mg.), in ether (1 ml.) was added to concentrated sulphuric acid (1 ml.) at 0° . The mixture was stirred at room temperature overnight, allowing the ether to evaporate. Dilution with water, followed by ether extraction, gave a neutral fraction consisting of a complex mixture, with no starting material present.

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PART II

STUDIES IN THE 3-AZABICYCLO (3.3.1) NONANE SYSTEM

INTRODUCTION

The 3-azabicyclo (3.3.1) nonane system (1) constitutes the nitrogen - containing part of the ring skeleton of the diterpene alkaloids¹, e.g., atisine (2), veatchine (3) and cuauchichicine (4). It also exhibits structural similarities to other azabicyclo (3.3.1) nonane derivatives, some of which occur naturally, e.g. pseudopelletierine (5).

Theoretically, the 3-azabicyclo (3.3.1) nonane system (1) can be synthesised in two ways, viz, condensation of the nitrogen- containing bridge to a cyclohexane ring in the 1,3-positions (6), and construction of the carbocyclic ring by attachment of a three-carbon unit to a 3,5-disubstituted piperidine (7).

In practice, however, route (6) offers wider preparative scope. 3-azabicyclo (3.3.1) nonane (1, R=H) was first obtained in 1932 by Komppa², by reduction in low yield of hexahydroisophthalimide at the lead cathode. The imide was prepared by distillation of the diammonium salt of cis/trans hexahydroisophthalic acid (8). Since only the cis form would be expected to undergo cyclisation, it appears that under the reaction condition the trans form is converted into the cis form.

This method has found most application in the synthesis of 3-substituted derivatives of (1), some of which possess hypotensive activity. Rossi et al³ prepared 1 (R=H), which on N-alkylation formed the compounds (9). Treatment of (8) with methylamine, followed by reduction of the resultant imide, gave 1 (R=Me)³, which was converted into its 2-dimethylaminomethyl

derivative⁴. The corresponding 5-derivative was also synthesised⁴. Condensation of 1 (R=H) with acrylonitrile and simple epoxides⁵, and reaction of the anhydride of (8) with dialkylaminoalkylamines^{5,6} yielded a variety of compounds of type (10). Rice and Grogan⁷ synthesised a number of compounds of type (11) by the latter route.

Concomitant work by Schneider and Götz^{8,9} afforded 1(R=Me, Et, CH₂Ph) by reacting (8) with primary amines, followed by reduction of the imide in high yield with lithium aluminium hydride (the reducing agent employed in all the more recent reports). Similarly, Leonard et al.¹⁰ prepared 1(R=CH₂CH₂OH) from 2-aminoethanol and either the dimethyl ester of (8), or the ditosylate (12).

An important method of accomplishing route (6) makes use of the Mannich reaction. Heterocyclic bicyclic compounds of the pydine¹¹(13) and bispidine¹² (14) type have been made in this way from pyridone - and pyrone- α,α' - diesters, methylamine and formaldehyde by Mannich et al. In 1957, Weatherbee et al.¹³ attempted unsuccessfully to prepare isopseudopelletierine (15) by condensation of cyclohexanone with formaldehyde and methylamine, only the diketoamine (16) being isolated.

In 1959, however, Blicke and McCarty¹⁴, using the more activated cyclohexanone - 2,6- diesters, prepared the 1,5-diester (17) in good yield. The trihydrochloride of (18) was similarly obtained¹⁴ from the corresponding diaminocyclohexanone¹⁵. At the same time, the diester (17a) was synthesised by Schneider and Götz^{16,9}, who hydrolysed

and, surprisingly, decarboxylated it to (15), Wolff-Kishner reduction of which afforded 1(R=Me), identical to the compound made by reduction of the corresponding imide. In 1962, House et al.¹⁷ succeeded in synthesising (15), albeit in low yield, by Mannich condensation of cyclohexanone. Another product was found to be the diketamine (16).

In their synthesis of isopseudogranatoline (19), Rossi and Butta¹⁸ prepared the derivatives (20a-d) of (15) by means of the Mannich reaction on 2-substituted and 2,6-disubstituted cyclohexanones. Each product on treatment with acid furnished (15), which was reduced by sodium borohydride and oxidised by potassium permanganate to (19). The similar bicyclic aminoketones (20d-g) were synthesised by Shimizu et al.^{19,20} during investigations on a total synthesis (vide infra) of the skeleton of the atisine series of alkaloids.

The preparation of the derivatives (22) of (15) by Becker²² is the only example of route (7). The 1,2,3-trisubstituted 4-piperidones (21) on treatment with methyl vinyl ketone in the presence of triethylamine afforded the bridged azabicyclic ketols (22) in high yield. This is a synthetic method commonly used to prepare carbocyclic bicyclic systems. Treatment of (22) with sodium methoxide effected retroaldolisation and re-cyclisation to the decahydroisoquinolines (23).

There have been two reports of syntheses of a partial skeleton of the diterpene alkaloids (24). Mercuric acetate oxidation of 1(R=CH₂CH₂OH) (vide supra) yielded the tricyclic oxazolidine (25), used by Leonard et al.¹⁰ as a simple model of the A,E,F-ring system of

the hexacyclic diterpenoid alkaloids. In (25), there was no steric driving force to the rearrangement of the oxazolidine ring which occurs in these alkaloids, e.g., atisine (2) and isoatisine (26). The model (25) served to define the stability towards isomerisation, and the base strength and other properties of the tricyclic ring moiety in (24) when freed from the steric influence of the remaining rings B,C and D.

The starting material in a synthetic approach to diterpenoid alkaloids by Shimizu et al.^{19,21} was (20f) (vide supra). A cis/trans mixture of the tetrahydrophenanthrene derivatives (27) was eventually obtained (Scheme 1). Since atisine-type alkaloids possess an A/B-trans conformation, only the trans isomer of (27) would be of use in further elaboration to the diterpene alkaloids.

Stereochemical studies have been carried out on derivatives of (1) using chemical and physico-chemical techniques. House et al.¹⁷ concluded that the absence of irregularities in the infra-red and ultra-violet spectra of (15) suggested that there was no appreciable interaction between the amine and carbonyl functions. Also, a series of three peaks in the infra-red spectrum of (15) in the 2600-2800 cm.⁻¹ region indicated²³ that the favoured conformation had at least two hydrogen atoms trans and coplanar with the unshared electron pair on the nitrogen atom. The N-methyl group must, therefore, be equatorial as in (28). Dipole moment and pK_A data¹⁷ were also in accord with (28). Studies of the decarboxylation²⁴, reduction²⁵, reaction

with organometallic reagents²⁶, N-alkylation²⁷ and solvolysis²⁸ of (15) or its derivatives added further evidence for the predominance of the chair-chair conformation.

Pumphrey and Robinson²⁹ deduced from proton magnetic resonance studies on 7-t-butyl derivatives (29) of (1) that both the carbocyclic and the heterocyclic rings were in the chair conformation (30). The configuration of the nitrogen atom was established by the presence of infra-red absorption similar to that observed by House¹⁷. In the two-chair conformation, this was possible only if the unshared electron pair was in the extremely hindered endo position, proving that the unshared electron pair is smaller than the hydrogen atom bonded to nitrogen.

Dobler and Dunitz³⁰ reported an X-ray structure analysis of the hydrobromide of 1(R=H) and stated that the cation had a chair-chair conformation in which the bond angles deviated somewhat from their ideal values, presumably because of steric repulsion between a pair of non-bonded hydrogen atoms. Nuclear magnetic resonance studies by McKenna et al.³¹ indicated that for the hydrochloride of 1(R=Me) in solution, the main configurational isomer had the chair-chair conformation (31). The corresponding methiodide was, however, apparently almost exclusively boat-chair (32).

Fairly recently another synthetic route involving the Mannich reaction has appeared. Investigations on the reaction of nitroaromatic

compounds with sodium borohydride by Severin et al.³²⁻³⁴ included the postulation that reduction of the metadinitrobenzenes (33) by sodium borohydride formed the di-sodium salt (34)³³, which on acidification afforded (35)³³. Treatment of (34) with formaldehyde and piperidine gave (36)³⁵, the structures being proved by conversion of 36(R=Me) to the toluidine (37), which was prepared by an independent synthesis. Mannich condensation of (34) with formaldehyde and methylamine produced in reasonable yield the 1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) nonenes (38)³⁵. The structures (38) were assigned mainly by analogy; the actual evidence presented was meagre, viz, analytical figures, ultra-violet absorption below 210 μ , unchanged in alkaline solution, and (in two cases) approximate molecular weight determinations.

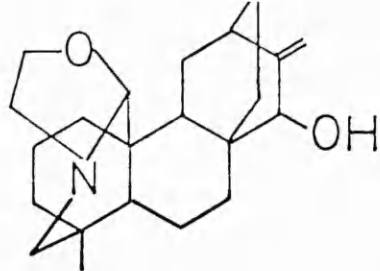
Similar products (39) and (40) were later obtained in low yields from (34) and the corresponding salt of 3,5-dinitroanisole respectively, and a Grignard reagent (R^1MgBr), formaldehyde and methylamine³⁶. Apart from the proof mentioned above, the compounds exhibited absorption in the infra-red at 1540cm^{-1} (nitro group) and since no silver chloride was formed by treatment of 39 ($R=Cl$) with alcoholic silver nitrate, the chlorine atom was stated to be vinylic. More complete spectroscopic proof was included in a later study, in which 2,4-dinitrophenol in the presence of sodium ethoxide reacted with acetone to form the salt (41), which gave the bicyclic compound (42) on reaction with methylamine and formaldehyde³⁷. Cyclohexanone

behaved analogously to form (44) via (43) ³⁷. Sodium borohydride reduction of (41) and (43) to (45) and (46) respectively, followed immediately by Mannich condensation, yielded not the expected products, but the tricyclic compounds (47) and (48).³⁷

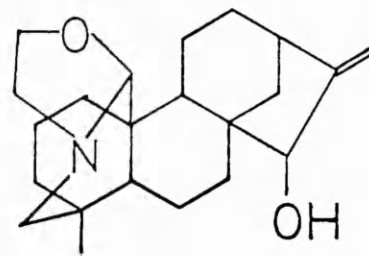
Previously mentioned examples of Mannich reactions used in route (6) involved activation by carbethoxy groups of the sites of Mannich condensation, whereas Severin's novel procedure made use of activation by nitro groups in salts such as (34). These salts promised to be of wide synthetic utility in the preparation of bridged bicyclic systems with a nitrogen atom at each bridgehead. It was therefore decided to seek proof of the structures (38) using rigorous chemical and spectroscopic means, and to examine thoroughly the scope of the reaction sequence leading to them.



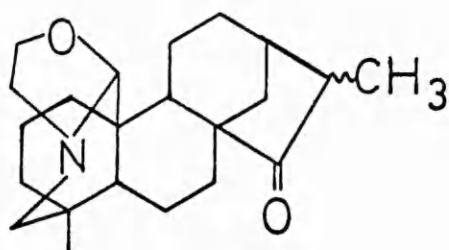
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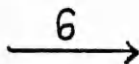
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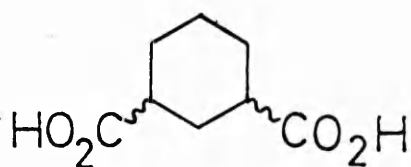
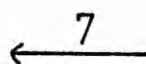
4



5 $R = CH_3$



1



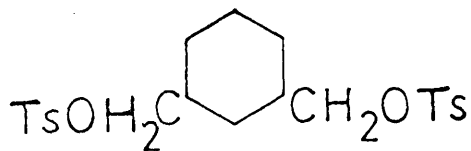
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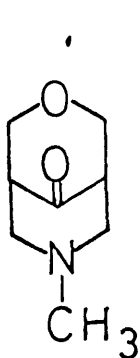
9 $R = \text{Ac, Et, } i\text{-Pr, } n\text{-Bu, NO, } CH_2\text{-CH=CH}_2$
 10 $R = (CH_2)_nNR_2$



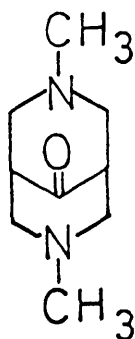
11 $R = H, CH_3, n-Bu, (CH_2)_nNMe_2, (CH_2)_nNEt_2, n = 2, 3$



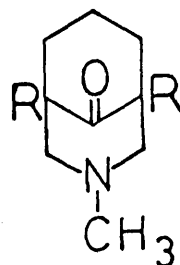
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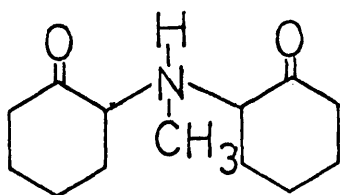


15 $R = H$

17a $R = CO_2Et$

17b $R = CO_2CH_3$

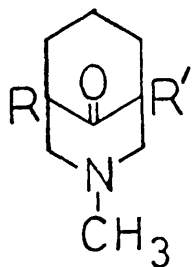
18 $R = CH_2NMe_2$



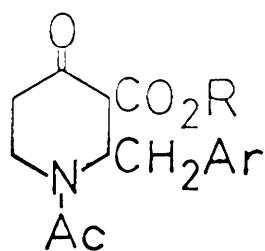
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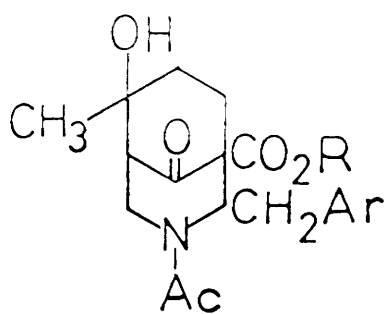
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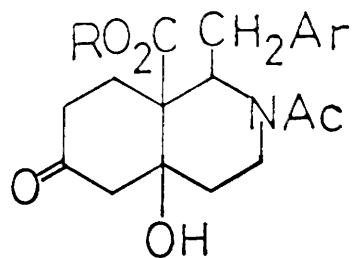
		R	R'
20	a	CO_2Et	
	b	$CONHPh$	
	c	H	$CONHPh$
	d	H	CO_2Et
	e	CH_3	CO_2Et
	f	CH_3	$C_6H_4OCH_3-p$
	g	CH_3	$C_6H_4OCH_3-m$



21



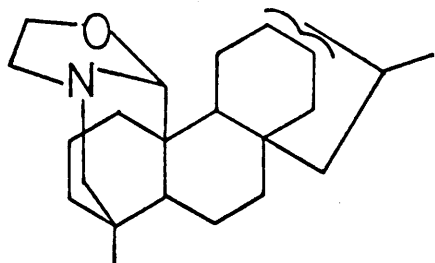
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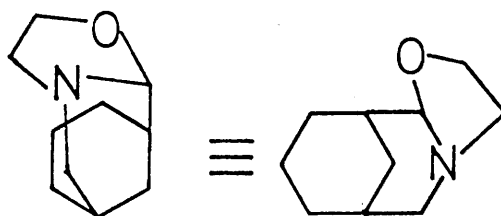
23

R = CH₃
t-Bu
CH₃
CH₃

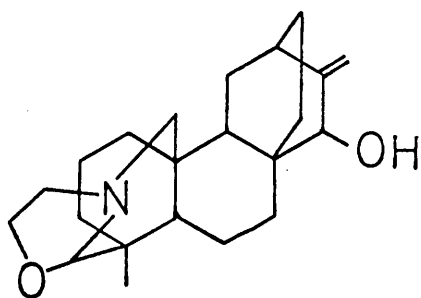
Ar = Ph
Ph
C₆H₄OCH₃-p
C₆H₃(OCH₃)₂-3,4



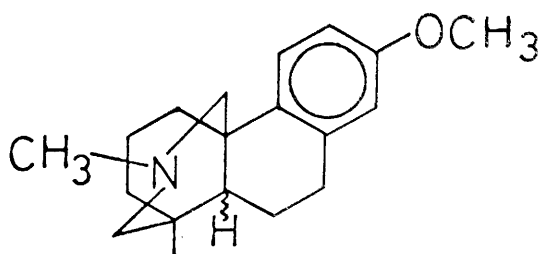
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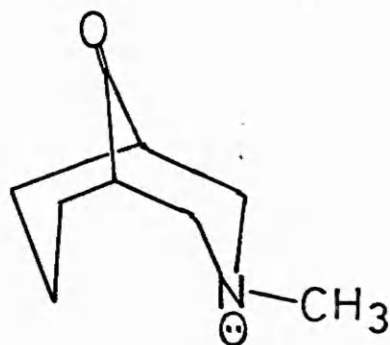
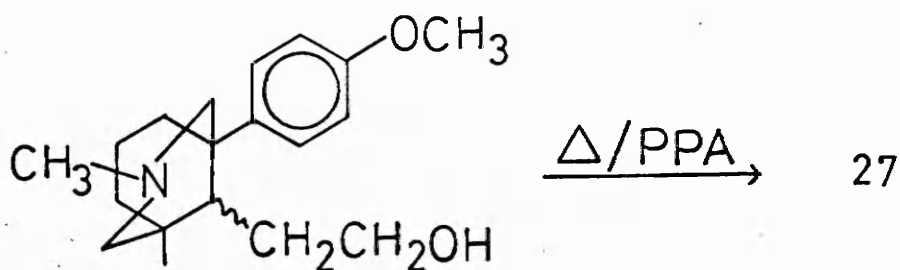
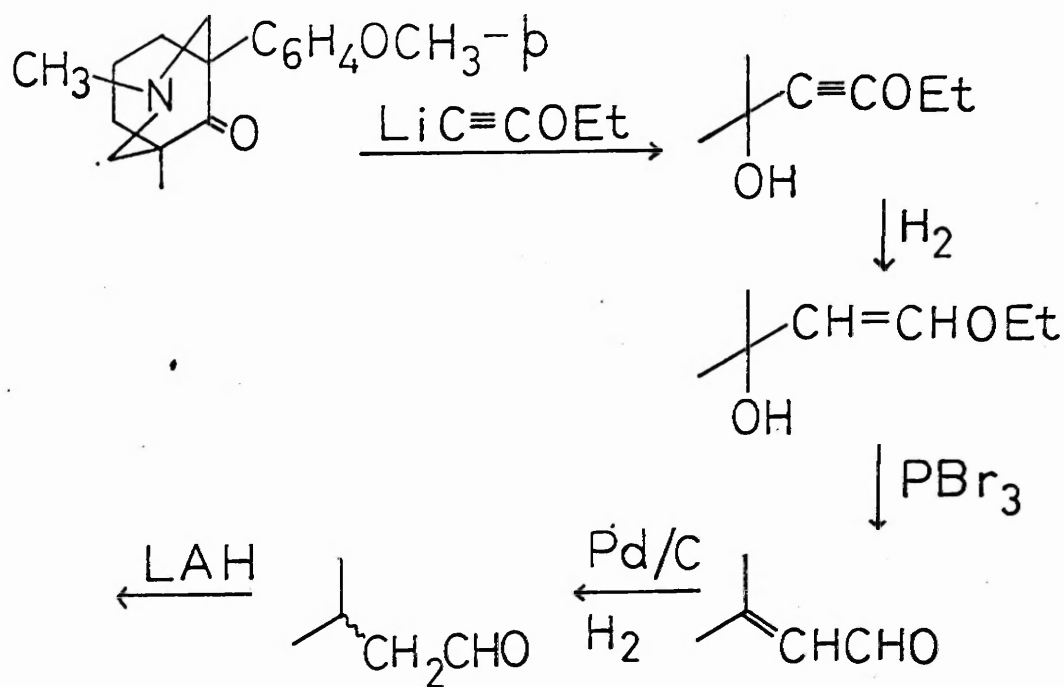


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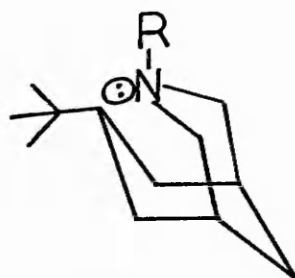
SCHEME 1



28

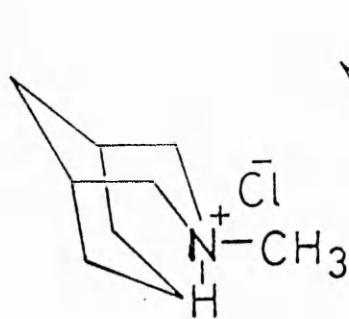


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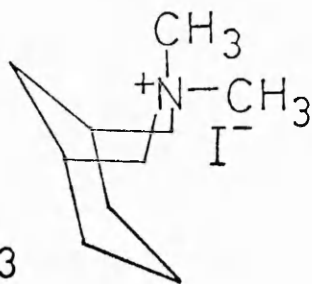


30

$\text{R} = \text{H}, \text{CH}_3$



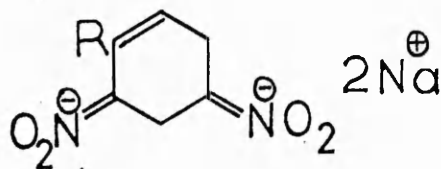
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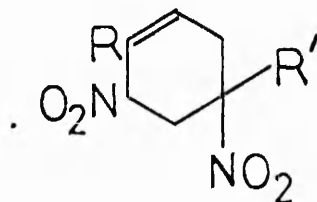
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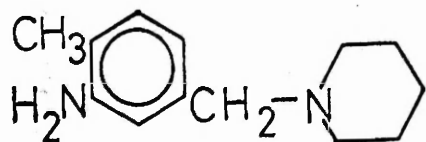


34

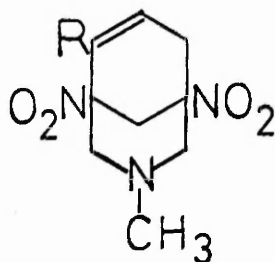


35 R=CH₃, Br, CH=CHPh, CO₂H
R'=H

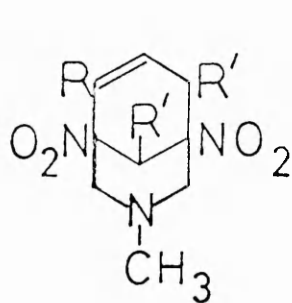
36 R= as above
R'=CH₂-N



37



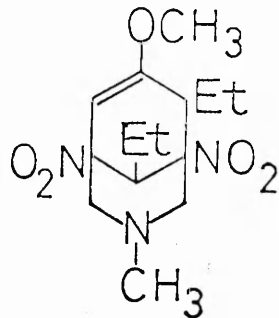
38 R=H, CH₃, Cl, CH=CHPh



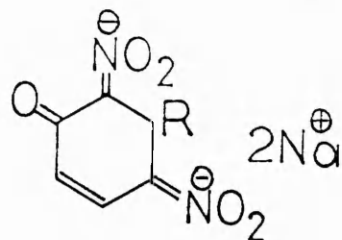
39

$R=H, R'=CH_3, Et, n-Bu$

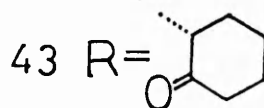
$R=Cl, R'=Et$



40

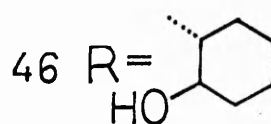


41 $R=CH_2COCH_3$

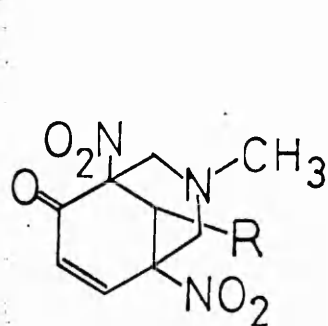


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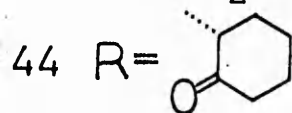
45 $R=CH_2CH(OH)CH_3$



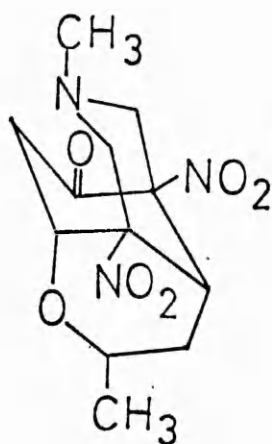
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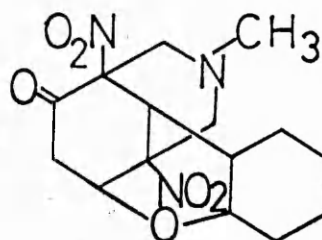
42 $R=CH_2COCH_3$



44



47



48

DISCUSSION

It was firstly necessary to repeat the procedure of
35
Severin et al. for the preparations of the known 1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) non-6-enes (1a), (1b) and (1c), in order that their structures might be confirmed by rigorous chemical and spectroscopic methods. Hence were obtained crystalline compounds, with melting points in agreement with those reported. Moreover, their mass spectra indicated the expected molecular weights of 227, 241 and 261 (263) for (1a), (1b) and (1c) respectively, and also contained peaks which confirmed the presence in each compound of two nitro groups (Table II). Further evidence for the proposed structures was available from their IR spectra (Table I), which exhibited bands at ca. 2800 (N-methyl), 1550 (asym. nitro) and 1340 (sym. nitro) cm^{-1} . In the case of (1c), doublets for the nitro group frequencies at 1562, 1552 and 1368, 1343 cm^{-1} could be attributed to interaction of the chlorine atom with the adjacent nitro group. A peak due to the double bond of (1c) was also observed at 1555 cm^{-1} . However, the NMR spectra (Table I4) of (1a), (1b) and (1c) presented somewhat conflicting evidence. Although those of (1b) and (1c) appeared to be in accord with the proposed structures, that of (1a) contained a sharp singlet in the olefinic proton region at 3.89 (2H), and a broad singlet in the allylic proton region at 7.20. This observation cast doubt on structure (1a), and prompted an extension of Severin's procedure to the syntheses of a

series of compounds of types (1) and (2), so that a more detailed examination of their NMR spectra could be made.

2,4-Dinitroanisole yielded after sodium borohydride reduction and Mannich reaction, 30% of crystalline material, analysing for $C_{10}H_{15}N_3O_5$, and with the correct molecular weight of 257 (mass spectrum). Its IR and NMR spectra appeared to confirm the presence of the bicyclic vinyl ether (1d). The former exhibited the peaks expected for N-methyl and nitro groups, with additional absorption at 1680 cm^{-1} ($C=C$). The latter included a triplet at 5.13 (1H, $J=4\text{c/s}$, olefinic proton), a doublet at 7.15 (2H, $J=4\text{c/s}$, allylic proton), a singlet at 6.45 (3H, methoxyl protons), and a singlet at 7.58 (3H, NCH_3). In contrast with this spectroscopic data, the chemical behaviour of this compound was not that expected of a vinyl ether, since only starting material was recovered after heating with dilute acid. With concentrated acid, no product at all was obtained. A probable explanation of the latter result was that the unstable intermediate ketone (3) decomposed to the water-soluble aminoacid (4).

From the appropriate m-dinitrobenzenes were prepared (1e), (1f), (2a), (2b) and (2c). Correlation between two compounds of type (2) was provided by esterification of the acid (2a) to yield crystalline material identical to the ester (2b). Considerable variations in yield were observed between compounds of types (1) and (2). The 7-substituted compounds (2) were available in much higher yields than the 6-substituted

analogues (1), e.g. 7-CO₂Et, 7-CO₂Me, 98%; 6-CO₂Et, 4%; 7-OMe (vide infra), 66%; 6-OMe, 30%. Stability was not however related to structure (1) or (2). On exposure to light, (1a) and (1d) were rapidly yellowed, whereas (2b), (2c) and (2d, vide infra) remained unaffected even after longer exposure.

Only the product from 2,4-dinitrophenol was not of the expected type. Hot ethanolic extraction of the crude reaction product, followed by recrystallisation, gave ca. 1% of colourless needles analysing for C₉H₁₆N₄O₄. The mass spectral molecular weight of 244 was in accord with the analytical figures. The presence of two nitro groups was shown by peaks at 198 and 152 m/e, corresponding to losses of 46 (NO₂) and 92 (2NO₂) m/e. The extra nitrogen atom implied by the analytical data was confirmed by the IR and NMR spectra. Peaks at 2812 and 2798 cm.⁻¹ in the IR were attributed to two N-methyl groups, and those at 1551 and 1353 cm.⁻¹ to nitro groups. The NMR spectrum contained a singlet at 7.64 (6H, two NCH₃), and an AB quartet at 7.13 (J=11c/s, bridge protons) with an overlapping signal at 7.34 (10H in all, 4 NCH₂). These data were fully consistent with the bispidine structure (5), the probable mode of formation of which is outlined in Scheme A. The instability of a molecule possessing a carbonyl group adjacent to a nitro group was reported by Severin et al., who found that the sodium salt (6) of picric acid, on reduction with sodium borohydride, followed by acidification, gave the acyclic

compound (7) (Scheme B). Similar reactions are known in the literature, e.g., the formation of 1,5-dinitropentane by acid treatment of the mono-potassium salt (8) of 2,5-dinitrocyclohexanone.⁴³

A detailed examination of the spectra of these compounds was now undertaken.

The IR spectra (Table 1) of both types (1) and (2) showed N-methyl absorption at 2790-2800 cm^{-1} . Absorption due to the double bond fell in the range 1655-1665 cm^{-1} , except when R=OMe (1680 and 1669 cm^{-1} for (1d) and (2e) respectively). Some compounds of type (1) exhibited a doublet ($\Delta \nu$ 6-14 cm^{-1}) for the asymmetric nitro group frequency in the 1550 cm^{-1} region, indicating interaction of the group R (Cl, OMe, CO₂Et, CO₂H) with the adjacent nitro group. The doublet observed in the ester carbonyl region for (1f), (R=CO₂ Et) was also explicable on this basis. In contrast, compounds of type (2) exhibited only single peaks in the 1550 cm^{-1} region. The symmetric nitro group frequency was observed as either a single band at 1340-1350 cm^{-1} , or a doublet at ca. 1365 and 1345 cm^{-1} , with no apparent correlation with structure type (1) or (2). Bohlmann bands in the 2600-2800 cm^{-1} region²³, which indicate that the favoured conformation has at least two hydrogen atoms trans and coplanar with the unshared electron pair on the nitrogen atom, were not observed.

All the mass spectra (Tables 11 and 12) contained peaks corresponding to losses of 46 (NO₂), 47 (HNO₂), 92 (NO₂ from P-46) and

93 (HNO_2 from P-46) m/e , and a peak at 91 m/e , probably due to the ion C_7H_7^+ (compounds without the double bond (Table 13) did not exhibit this peak). In most cases, losses of 30 (NO) and 60 (NO from P-30) were also observed. The (P-1) peak (loss of a hydrogen atom), which has been reported⁴⁴ as being characteristic of N-methyl piperidines, was not present. Mass spectrometry hence confirmed the presence of two nitro groups, as well as identifying the substituent R.

The NMR spectra of compounds of type (1), ($\text{R} \neq \text{H}$) exhibited a triplet ($J=4\text{c/s}$) in the olefinic proton region, and a doublet at ca. 7.1 ($J=4\text{c/s}$) for the allylic protons. In the case of (1b), these signals were observed as multiplets with half-band widths of 7-8c/s (Table 14). The 7-substituted compounds (2) showed broad singlets for the olefinic and allylic protons, each with the same half-band widths (Table 15).

As mentioned above, the olefinic protons of (1a) resonated as a sharp singlet at 3.89, and the allylic protons as a broad singlet at 7.20, which raised doubts as to the correctness of the proposed structure. Similar signals were present in the spectra of (34) and the picrate of (35), which were prepared later (Table 16). In trifluoroacetic acid, the olefinic protons of (1a) and (34), (Table 17), gave rise to doublets at 3.75 and 3.70 (each $J=6\text{c/s}$) respectively. In benzene (Table 18), finer splitting was observed for (1a). The C6 proton gave a doublet at 4.43 ($J=2.3\text{c/s}$), and the C7 proton a triplet at 4.67 ($J=3\text{c/s}$), each superimposed

on a multiplet. It thus appeared that in CDCl_3 , the sharp singlet observed for the olefinic protons on the unsubstituted double bond was due to accidental equivalence.

The singlet due to the N-methyl protons appeared in the range 7.53 - 7.62 for compounds of types (1) and (2).

Difficulty was experienced initially in assigning the absorptions due to the four NCH_2 protons. It was considered that by comparing the NMR spectra with those of the corresponding picrates, the NCH_2 proton signals could be identified by their known downfield shift⁴⁵ in the picrate relative to the parent amine. The picrates of (1a)-(1d), (1f), (2b) and (2c) were prepared, but after several recrystallisations, these rather insoluble derivatives still exhibited a m.p. range of ca. 10° . However, the picrate of (35), which had a m.p. of $134-144^\circ$, was later found to analyse correctly.

With the exceptions of those of (1c) and (2b), these picrates were almost totally insoluble in CDCl_3 . The two soluble picrates however gave signals identical to those of the parent base, in addition to a singlet at 0.80 (2H, picrate anion aromatic H). This was a surprising result, since work in this department had revealed considerable shifts (ca. 0.7 ppm) for the α proton signals in the picrates of Mannich bases.⁴⁵ It was therefore decided to initiate a study of the NMR spectra of simple amines and their picrates, in order to elucidate the reasons for the observed shifts. A common solvent (CDCl_3)

was used throughout in the expectation that any solvent shift would be eliminated, and a more regular displacement pattern might emerge. In fact, the results (Table19) showed a pattern very similar to that reported.⁴⁶ Tertiary amines showed a larger shift than secondary amines. In the former, $\Delta(\alpha\text{CH}_2)$ was ca. 0.75 ppm., in the latter, 0.48-0.54 ppm. Displacements of βCH signals, where they could be identified with certainty, were smaller (ca. 0.3 ppm). In one case (Et_3N , Table20), the hydrochloride was found to show similar shifts to the picrate, suggesting that the aromatic ring played no part in the deshielding, which must be entirely due to N-protonation. With this amine, similar shifts were observed in D_2O as in CDCl_3 (Table20).

Since the picrates of (1c) and (2b) did not show these shifts, it was considered possible that in CDCl_3 solution dissociation might have taken place, resulting in a mixture of picric acid, and the tertiary amine. Evidence for this came from the NMR signal due to the picrate anion aromatic protons. In the simple amine picrates, this signal occurred at 1.1, whereas in the supposed picrates of (1c) and (2b), singlets at 0.80 were observed. Since for picric acid, the aromatic signal occurred at 0.80, NMR spectroscopy seemed to confirm the presence of picric acid.

In contrast, material precipitated from CDCl_3 solutions of the picrates of (1c) and (2b) possessed melting points in the same ranges as the picrates. These melting points were far higher than that of

picric acid. Either complex absorption or a pair of broad singlets at 7.2 - 7.7 was eventually assigned to the NCH_2 protons.

The geminal bridge protons of the compounds (1), (R_2H), appeared as a pair of broad singlets at ca. 6.6 and 6.8 (J ca. 12c/s). The compounds(2) and (1a) gave apparent triplets at ca. 6.8 (J ca. 11c/s), presumably due to overlapping of the two inner peaks of the AB quartet. In two saturated compounds later prepared, an apparent doublet (J=12c/s), each signal slightly split, was present. This was considered to arise by interchanging of the two inner peaks (Table 22). This signal, shifted considerably downfield by the two nitro groups, varied little in position in all the compounds studied.

The preparation of 1,3,5-trinitrocyclohexane (9) by sodium borohydride reduction of sym-trinitrobenzene (TNB) has been reported by Severin et al.³² Since comparison of its spectra with those of compounds (1) and (2) would be of interest, the published procedure was repeated, yielding a highly unstable red oil, consisting mainly of one compound (cf, (9) was reported as having m.p. 125°). This material was probably crude (9), since absorption in the IR occurred at 1563 cm^{-1} (NO_2 asym. str.). Such compounds are known to be unstable, e.g., it was observed by Nielsen⁴⁷ that 1,3-dinitro-cyclohexane was unstable under basic conditions.

Similar reduction of TNB, followed by treatment with formaldehyde and methylamine, did not afford the bicyclic trinitro

compound (10). The basic fraction of the product exhibited nitro, N-methyl, and also weak hydroxyl absorption in the IR, and although shown by TLC to consist mainly of one compound, it could neither be induced to solidify, nor could a solid picrate be prepared.

It had therefore been demonstrated that the reduction - Mannich sequence was applicable to a wide range of substituted m-dinitrobenzenes. p-Dinitrobenzene, by analogous behaviour, would be expected to form the 3-azabicyclo (3.2.2) nonene (11). However, no violet coloration (characteristic of the m-dinitrobenzenes) was formed on addition of sodium borohydride, and after treatment with formaldehyde and methylamine, the small basic fraction formed was found to contain none of the desired compound (11). Although similar treatment of o-dinitrobenzene was not investigated, it seems feasible to state that this reaction sequence is limited solely to meta-substituted dinitroaromatic compounds.

Although further extensions in the scope of this sequence were carried out (p.87) it is pertinent at this point to detail the chemical studies on compounds of types (1) and (2) which served to provide added proof of structure.

Hydrogenation of (1a) with 10% palladium on charcoal in ethyl acetate furnished 37% of the saturated compound (12), after chromatographic separation from more polar products. The mass spectral molecular weight of 229, and the lack of olefinic proton resonance in the

NMR spectrum, and of double bond absorption in the IR spectrum, confirmed the presence of one double bond in (1a).

Efforts were next directed at the degradation of (1a) by oxidative cleavage of the cyclohexene ring to form a 3,5-dinitro-N-methyl piperidine. Accordingly, an aqueous suspension of (1a) and selenium dioxide ⁴⁸ ~~were~~ heated at reflux for 18 hours, but, despite various extraction procedures, only about 20% of material was recoverable. The main component, isolated in ca. 10% overall yield, was a colourless crystalline compound, m.p. 68-9°. A singlet at 0.37 (1H, formyl proton) and a doublet at 3.62 (2H, J=6.5c/s, olefinic protons ~~on a cis double bond~~) in the NMR spectrum indicated the presence of an unsaturated aldehyde. An AB quartet at 6.10 (2H, J=12c/s) showed that the bridge methylene had remained intact. No signal was observed in the 7.6 region (NCH₃). Remaining peaks at 6.89 (singlet, 4H) and 7.13 (broad singlet, 4H) were not assigned. IR spectroscopy confirmed the above observations, viz., no N-methyl absorption, and peaks at 1702 (α,β -unsaturated aldehyde C=O) and 1551 cm.⁻¹ (asym. NO₂ str.). UV absorption occurred at $\lambda_{\text{max}}^{\text{EtOH}}$ 227 m μ (e3600), (cf, crotonaldehyde, λ_{max} 217 m μ , e17900).⁴⁹ The material analysed for C₉H₁₄N₂O₄ (mol. weight 214), in disagreement with the mass spectral molecular weight of 242. However, no peaks could be accounted for by loss of NO₂ or NO, and the spectra of two later products, although identical as far as 170 m/e, had different

parent ions. Although soluble in dilute hydrochloric acid, it did not form a picrate. Positive Fehling's and silver mirror tests were however observed. Two structures, neither of which was compatible with the foregoing conflicting evidence, were briefly considered. The aldehyde (13), $C_9H_{13}N_3O_5$, (243), the formation of which is rationalised in Scheme C, however possessed a N-methyl group. The amide (14), $C_9H_{11}N_3O_5$ (241), arising by oxidation of the N-methyl group, would be expected to have a NMR singlet at ca. 2.0 (cf, $HCOONMe_2$, 2.16), and an IR band in the range 1670-1630 cm^{-1} (tertiary amide $C=O$). A satisfactory structure for this product was not obtained.

It was decided to employ a less random method of cleaving the double bond of (1a). Hydroxylation of (1a) with osmium tetroxide by the procedure of Baran⁵⁰ yielded 93% of the 6,7-cis-diol (15), $C_9H_{15}N_3O_6$. The mass spectrum showed the correct molecular weight of 261, with peaks corresponding to losses of 17(OH), 18(H_2O), 46(NO_2), 92($2NO_2$) and 93(NO_2 and HNO_2) m/e. The loss of 17 m/e may have arisen by the breakdown process depicted in Scheme D. The diol exhibited the expected IR absorption (hydroxyl, N-methyl and nitro). Due to insolubility in deuteriochloroform, the NMR spectrum was run in trifluoroacetic acid, but apart from a singlet at 6.71 (NCH₃), assignments could not be made.

Treatment of the diol (15) in methanol with sodium metaperiodate

in a nitrogen atmosphere, afforded a **brown semi-solid oil**, which showed hydroxyl, N-methyl, nitro and carbonyl (1720 cm.^{-1}) absorption in the IR. Careful recrystallisation yielded an unstable pale-brown crystalline solid with a mass spectral molecular weight of 231.

Significant peaks in the mass spectrum were at 230 (P-1) and 214 m/e (P-17, loss of OH), (the latter probably arising by a process similar to that in Scheme D), as well as those indicating the presence of two nitro groups. Absorption in the IR (CHCl_3) occurred at 3595 (sharp peak, free hydroxyl), 2805 (N-methyl), 1549 (asym. NO_2) and $1371\text{ (sym. NO}_2\text{) cm.}^{-1}$ The carbonyl region was transparent. These data were compatible with the 3-azabicyclo (3.2.1) octane alcohol (16), formed by loss of formic acid from the intermediate dialdehyde (17), followed by cyclisation (Scheme E). The IR carbonyl absorption in the crude product could then be attributed to the dialdehyde (17). NMR assignments were made as follows:-

Multiplet at 5.5 (1H, half-band width ca. 12c/s, C_6 carbinyll proton); an apparent triplet at 6.73 (2H, $J=10\text{c/s}$, bridge protons); 7.42, ca. 7.6 (NCH_2), and singlet at 7.59 (1OH in all, NCH_3). The alcohol (16) was too unstable to be prepared analytically pure, and on standing was decomposed to amorphous material insoluble in chloroform. Since the odour of nitrous acid was detectable, the decomposition pattern was probably as outlined in Scheme F.

The hydroxyl group of (16) was shown to be extremely hindered

by the recovery of unchanged (16) after treatment with excess Jones reagent. At this point, it was planned to convert the tosylate of (16), by treatment with refluxing collidine,⁵¹ to the olefin (18), oxidation of which would afford the desired 3,5-dinitro-N-methylpiperidine. In the event, exposure of (16) for 16 days to tosyl chloride in pyridine gave a product, the IR spectrum of which showed only very weak tosylate peaks at 1600 cm^{-1} and in the fingerprint region. TLC analysis detected only starting alcohol.

Conclusive proof of the structure of the alcohol (16), and correlation between the compounds (1a) and (1b), was afforded by similar hydroxylation of the olefin (1b). The resultant crystalline diol exhibited IR and NMR absorption consistent with structure (19). In particular, the NMR multiplet at 5.45 (1H), due to the C7 carbinyll proton, had a half-band width of 18c/s, demonstrating⁵² that this proton was axial, i.e., the C7 hydroxyl group must be equatorial (exo).

Reaction of the diol (19) with sodium metaperiodate gave, after chromatographic separation from unchanged diol, material identical to the alcohol (16) obtained from the diol (15). In this case, the intermediate ketoaldehyde (20) must have lost acetic acid prior to cyclisation to form (16).

Since the presence of the bridgehead nitro groups appeared to result in decreased stability, and undesired decompositions, it was decided to attempt their removal by deamination of the corresponding

triamine. The dinitro compound (1a) was therefore treated with excess lithium aluminium hydride⁵³ in refluxing THF, affording 63% of the triamine (21) as a yellow oil which darkened on standing. Owing to extensive tailing on TLC chromatograms, even in amine buffer solvents, the purity of this material could not be estimated. It however gave rise to IR absorption at 3350 (broad band, N-H str.), 3050 (=C-H str.), 2800 (NCH₃) and 1610 cm.⁻¹ (N-H def.). No nitro group absorption was present. Distillation proceeded only with large loss, and attempts at preparing solid derivatives proved unsuccessful.

A deamination procedure used by Berson and Ben-Efraim⁵⁴ was applied in an attempt to convert crude (21) to the diacetate (22). Overnight treatment of (21) with acetic acid and sodium nitrite gave a low yield of a dark yellow gum, which exhibited similar TLC behaviour and IR absorption to the starting material. An additional peak in the IR at 1730 cm.⁻¹ (acetate C=O) was however present. Several changes in reaction conditions led to similar products.

An alternative method due to Stetter and Goebel⁵⁵ was also employed. It involved sodium nitrite and aqueous acetic acid, and was used by them to convert an amine to an alcohol in high yield. Under these conditions, crude (21) however furnished material similar to that obtained before.

No 3-azabicyclo (3.3.1) nonan-7-ones have been reported in the literature, and since it was of interest to examine the nature of any

interaction between the amine and carbonyl functions in this bicyclic system, it was decided to attempt the synthesis of the aminoketone (23). Also planned was the preparation of the dibenzylidene derivative of (23), which by ozonolysis would afford the desired dinitropiperidine.

The first sequence aimed at (23) consisted of hydroboration of (1a), followed by oxidation. It was however anticipated that hydroboration⁵⁶ of the unsubstituted double bond of (1a) would result in the formation of a mixture of the alcohols (24) and (25). In contrast, the substituted olefin (1b) would be expected to yield solely the exo alcohol (26). Hence, the preferred starting material would be (1b). The alcohol (26) was accordingly prepared in low yield, after chromatographic separation from unreacted (1b). Only an IR band at 3623 cm.⁻¹ due to a free hydroxyl group, was present in this region. The NMR spectrum also pointed to an exo conformation for the 7-hydroxyl group, since the broad multiplet at 5.45 (1H, C7 carbinyll proton) had a half-band width⁵² of 20c/s (diaxial coupling of C7 proton with C6 and C8 protons).

Oxidation of the alcohol (26) with Jones reagent afforded a mixture of three compounds, having IR absorption at 1720 and 1680 cm.⁻¹ The low yield on hydroboration, and the formation of a mixture on oxidation, made it obvious that this route to (23) was unsuitable.

Unsaturated amides are known to undergo the Hofmann

rearrangement to yield ketones. In particular, Bell and Archer⁵⁷ have reported the preparation of 2-tropinone (27) by treatment of anhydroecgonine amide (28) with cold aqueous sodium hypochlorite⁴¹ in methanol, followed by acid hydrolysis. The unsaturated amide (2d) was therefore prepared from 3,5-dinitrobenzamide in good yield in the usual way. This stable crystalline compound analysed for $C_{10}H_{14}N_4O_5$, and showed the correct molecular weight of 270 from the mass spectrum. IR (nujol) bands at 3458 (free N-H str.), 3170 (bonded N-H str.), 1696 (amide I C=O), 1618 cm^{-1} (amide II C=O) and 1659 cm^{-1} (C=C str.) confirmed the presence of an unsaturated amide. In the NMR spectrum were observed a broad signal at 2.4 (2H, amide protons), a broad singlet at 2.84 (1H, olefinic proton), and a singlet at 6.65 (3H, N-methyl protons).

Low solubility in methanol of the amide (2d) necessitated the addition of a considerable amount of THF prior to the addition of the sodium hypochlorite solution. After treatment with dilute hydrochloric acid, a rather laborious procedure to remove unchanged amide furnished a clear red oil, a mixture of five compounds. The desired ketone (23) was isolated from the least polar band of the preparative thin layer chromatogram in an overall yield of 12% (based on consumed amide). The colourless needles analysed for $C_9H_{13}N_3O_5$, and exhibited the following NMR signals:- a triplet at 6.85 (2H, bridge protons), a singlet at 7.04 (4H, C6 and C8 protons), singlets at

7.21 and 7.40 (4H, NCH₂), and a singlet at 7.59 (3H, NCH₃). Under conditions in which cyclohexanone formed a bis-benzylidene derivative, the aminoketone (23) however yielded no product. Its IR spectrum had $\nu_{\text{C=O}}^{\text{CCl}_4}$ 1734 cm.⁻¹ and $\nu_{\text{C=O}}^{\text{CHCl}_3}$ 1727 cm.⁻¹ These unexpectedly high values prompted comparison with those of the ketones listed in Table 5. The observed $\nu_{\text{C=O}}$ for (23) of 1734 cm.⁻¹ is seen to be the highest of all the frequencies listed, although that of the dione (29), (1729 cm.⁻¹), and the highest value reported for the aminoketone (30) (1733 cm.⁻¹), are of the same order.

Leonard⁵⁸ found that in cyclic aminoketones such as (31), the carbonyl stretching frequency was decreased by transannular association of the carbonyl and amine functions (Scheme G). The IR spectra of the perchlorates of (31) were found to be transparent in the carbonyl region. The decrease became less as the group R became bulkier, since the increasing steric hindrance meant that the bicyclic form was less possible. Since $\nu_{\text{C=O}}$ for (23) was higher than that reported for the ketone (32) (1717, 1706 cm.⁻¹), it appeared that the opposite effect might be occurring, viz., a repulsion between the amine and carbonyl functions of (23). Unfortunately, (23) did not form a picrate. A comparison of its IR spectrum with that of (23) would have been of interest. The IR carbonyl stretching frequencies of some N-substituted analogues of (23), when compared with that of (23), might however serve to provide evidence for amine-carbonyl interaction. This is discussed later.

Further evidence for the chair-chair conformation of the

3-azabicyclo (3.3.1) nonane system (see introduction) was provided by examination of the IR and NMR spectra of the alcohol (33), $C_9H_{15}N_3O_5$, prepared in high yield by sodium borohydride reduction of the ketone (23). Very strong intramolecular hydrogen bonding in (33) was apparent from its IR spectrum (concentration independent absorption at $3450\text{--}ca. 3100\text{ cm.}^{-1}$). Moreover, the N-methyl peak at 2822 cm.^{-1} was at the highest frequency observed for any compound of this type. Both these facts illustrated the endo configuration of the 7-hydroxyl group. Confirmation of this was derived by measuring (in $CDCl_3/D_2O$) the half-band width⁵² of the NMR multiplet at 5.80 (1H) due to the C₇ carbonyl proton. The value of $11c/s$ showed the C₇ proton to be equatorial, i.e., the hydroxyl group was axial (endo). In agreement with this, the C₆ and C₈ protons resonated as a doublet at 7.63 (4H), with $J=3c/s$, the value expected for axial -equatorial and diequatorial coupling. In $CDCl_3$, the multiplet was much broader ($J_{base} 30c/s$), due to additional coupling with the hydroxyl proton. Indeed, the^{59,60} hydroxyl proton gave rise to a doublet at 2.9 (1H, $J=12c/s$), indicating that this proton was not undergoing rapid exchange, but was constrained by the nitrogen atom. The value of J pointed to a dihedral angle of $ca. 180^\circ$ between the carbonyl and hydroxyl protons, which agreed exactly with a model of (33) with the hydroxyl proton directed right at the amine nitrogen atom. (Scheme H).

At this stage, it was thought that the projected investigations

on further extensions of the reduction - Mannich sequence could be combined with a search for a synthetic route to N-substituted analogues of the ketone (23), in order that comparisons of carbonyl stretching frequencies could be made.

Accordingly, a series of amines were substituted for methylamine in the Mannich step. m-Dinitrobenzene, on reduction and treatment with formaldehyde and ethylamine, furnished 41% of a basic dark red oil, from which was obtained a low-melting crystalline solid. This material was shown to have the expected structure (34) by analysis ($C_{10}H_{15}N_3O_4$), mass spectrometry ($P = 241 \text{ m/e}$), and IR absorption at 1555 and 1353 cm^{-1} (nitro). As in the case of (1a), the two olefinic protons gave rise to a sharp NMR singlet at 3.98, and the allylic protons to a broad singlet at 7.26. The remaining signals due to the bridge, N-ethyl, and NCH_2 protons were all assigned (Table 16).

The use of benzylamine led to the formation in 12% yield of a basic dark red oil, which could not be obtained solid. It was shown however by its IR absorption (nitro, aromatic C=C and =C-H bands) to be the N-benzyl compound (35), and was characterised by its picrate, which analysed correctly for $C_{21}H_{20}N_6O_{11}$. The NMR spectrum of the picrate exhibited similar olefinic and allylic proton signals to those of (1a) and (34), (vide supra).

When ammonia was used as the amine in the Mannich step, the

basic fraction, obtained in 40% yield, was a dark yellow oil which partially solidified. The routine IR spectrum showed N-H absorption, and TLC, conducted in an amine buffer solvent, indicated the presence of two amines. By washing the oil with hot solvents, a straw-coloured solid with m.p. 132-140° which could not be further purified by recrystallisation, was obtained. This material had $\nu_{\text{max}}^{\text{Nujol}}$ 1562 and 1358 cm^{-1} (nitro), but no N-H str. band. However, it was later observed that other fully characterised N-H compounds of this type (vide infra) exhibited no band in the N-H str. region. This product was probably crude (36), since the NMR spectrum contained a singlet at 1.65 (1H, amine proton), a doublet at 2.46 (2H, $J=6\text{c/s}$, olefinic protons) and a broad singlet at 6.37 (NCH₂ protons). Its picrate had a wide m.p. range, which appeared to include two melting points. Indeed, TLC analysis of the picrate confirmed the presence of two compounds, but lack of solubility precluded the use of preparative TLC for their separation.

Unsuccessful attempts were also made to synthesise the N-phenyl and N-acetyl compounds (37) and (38) respectively, by substitution of aniline and acetamide for methylamine. In the former case, the small basic fraction contained aniline, and a mixture of three other compounds. In the latter case, the product, a mixture of two compounds, did not have IR absorption expected for a tertiary amide.

In contrast to m-dinitrobenzene, however, methyl 3,5-

dinitrobenzoate, after sodium borohydride reduction and treatment with formaldehyde and ammonia, afforded a good yield of a single crystalline compound, the methyl ester (39). This compound analysed for $C_{10}H_{13}N_3O_6$, and had $\nu_{\text{max}}^{\text{Nujol}}$ 1736 (ester C=O), 1664 (C=C), and 1276 cm^{-1} (C-O), in addition to nitro group absorption. Absorption due to N-H was however absent. Its NMR spectrum was found to be extremely similar to that of (2c), (both in $\text{CF}_3\text{CO}_2\text{H}$, Table 21), with a singlet at 1.64 (1H, amine proton) instead of one at 6.72 (3H, NCH_3). A broad singlet at 2.75 (2H) and a sharp one at 6.02 (3H) were due to the olefinic and methyl ester protons respectively.

By hydrogenation of (39) to the endo ester (40), followed by thermal cyclisation, it was hoped to synthesise the azaadamantane lactam (41), formation of which would constitute added proof of the double chair conformation of the 3-azabicyclo (3.3.1) nonane system (cf, the preparation of the alcohol (33)). Hydrogenation of an acetic acid solution of (39) over Adams' catalyst yielded a colourless viscous gum, which slowly darkened on standing, and was too insoluble for TLC analysis. Routine IR showed the absence of the double bond peak at 1655 cm^{-1} , but the presence of an unassigned band at 1635 cm^{-1} . Ester and nitro group absorption still remained. A nujol mull of this material was maintained for a short time at a temperature of 180-200°, which caused disappearance of IR ester carbonyl absorption. No IR band at ca. 1680 cm^{-1} expected for the lactam (41)

was however present. Removal of nujol left an intractable brown gum.

Similar reduction - Mannich treatment of 3,5-dinitrobenzamide furnished the bicyclic amide (42). So insoluble was this compound, that the analytical sample, $C_9H_{12}N_4O_5$, was prepared by washing the high melting (234-235°) solid with hot solvents. The unsaturated amide group was identified by IR (nujol) bands at 3458, 3410 (free N-H str.), 3190 (bonded N-H str.), 1680 (amide I C=O), 1602 (amide II C=O) and 1652 $cm.^{-1}$ (C=C str.). Absorption at 3525 $cm.^{-1}$ was tentatively assigned to the secondary amine function. It had been hoped that the desired aminoketone (45) would be available by application of the Hofmann reaction to this amide, but due to the extreme insolubility of the amide, this conversion could not be attempted.

It thus appeared that the sequence was of use only with primary amines such as methylamine, ethylamine and benzylamine, and in certain cases, with ammonia.

The preparation in good yield of the amide (42) from 3,5-dinitrobenzamide augured well for the syntheses of the amides (43) and (44), transformations of which to the aminoketones (46) and (47) were planned. However, the attempted preparation of (43) gave a crude red solid, which, by virtue of its IR spectrum, certainly contained the desired amide, but which resisted all attempts at recrystallisation. The amide (44) was not obtained pure. The usual

procedure afforded a yellow oil, which although exhibiting the IR absorption expected for (44), consisted of a complex mixture, and could not be purified.

The failure of this approach to the aminoketones (46) and (47) necessitated a search for an alternative route. It was envisaged that application of the aforementioned extensions of the Mannich step (to ammonia and other primary amines) to 3,5-dinitroanisole would render available the vinyl ethers (48), (49), and (50), hydrolysis of which would afford (45), (46) and (47) respectively. The feasibility of this sequence was firstly tested by preparing the vinyl ether (2e). This rather unstable crystalline compound, $C_{10}H_{15}N_3O_5$, possessed IR and NMR absorptions similar to those of other compounds of type (2), (Tables ¹ and ⁵ respectively). Quantitative hydrolysis occurred on heating with dilute acid, affording material identical to the ketone (23) derived from the amide (2d). This route to (23) was far superior to that previously followed. This ready hydrolysis of the vinyl ether (2e) contrasted with the anomalous stability of its isomer (1d).

With ammonia in place of methylamine, 3,5-dinitroanisole yielded a basic fraction containing two compounds, the less polar of which predominated. After separation by preparative TLC, the major product was found to be the N-methyl vinyl ether (2e), previously prepared. This was presumably formed by methylation of the desired N-H analogue (48) by formaldehyde. The more polar constituent, a pale yellow oil which

did not solidify, was obtained in 7% yield. Comparison with the spectral characteristics of (2e) confirmed the presence of the desired compound (48). IR peaks were observed at 3400 (liquid film, N-H str.), and at 1663 (C=C), 1550, 1366, 1339 (NO₂) and 1236 (=C-O, all in CHCl₃). A carbonyl impurity band at 1740 cm.⁻¹ was also present. A singlet at 7.93 (1H) in the NMR spectrum was attributed to the amine proton.

Yields of 10% and 24% of the N-ethyl (49) and N-benzyl (50) vinyl ethers respectively were realised by a similar route involving ethylamine and benzylamine. Neither of these rather unstable yellow oils was characterised analytically, but structural confirmations were carried out by means of IR and NMR spectroscopy. Their IR spectra contained all the absorptions mentioned above for (48), except for a peak at ca. 3100 cm.⁻¹ (=C-H str.) instead of that at 3400 cm.⁻¹. The NMR absorptions of the four vinyl ethers are assembled together in Table 23. In each case, the olefinic and allylic protons appeared as broad singlets at ca. 5.0 and 7.2 respectively, and the methoxyl protons as a singlet at ca. 6.4 (3H). Complex signals at ca. 7.4-7.7, and a triplet at ca. 6.80 (2H), were due to the NCH₂ and the bridge protons respectively.

On hydrolysis with dilute acid, the crude vinyl ether (48) furnished 70% of material with a broad carbonyl band at 1735 cm.⁻¹ (CHCl₃) in addition to secondary amine and nitro absorptions. This product, which was mainly one compound, the ketone (45), partially

solidified, but resisted purification by recrystallisation.

Hydrolysis of (49) and (50) afforded the desired aminoketones (46) and (47) in 75 and 70% yields respectively. The former ketone, $C_{10}H_{15}N_3O_5$, exhibited $\nu_{C=O}^{CCl_4}$ 1732 and $\nu_{C=O}^{CHCl_3}$ 1727 cm^{-1} , and the latter, $C_{15}H_{17}N_3O_5$, $\nu_{C=O}^{CCl_4}$ 1731 and $\nu_{C=O}^{CHCl_3}$ 1727 cm^{-1} . Comparison (Table 7) of the carbonyl stretching frequencies of the three N-substituted aminoketones (23), (46) and (47), showed that there was a negligible decrease in that order in the case of CCl_4 , but none in the case of $CHCl_3$. This strongly suggested that the amine and carbonyl functions at the 3- and 7- positions respectively in this system exerted no interaction on each other. The NMR resonances of the ketones (46) and (47) were similar to that described (vide supra) for the ketone (23), (Table 24). A quartet at 7.37 (2H, $J=7c/s$) and a triplet at 8.97 (3H, $J=7c/s$) confirmed the presence in (46) of an N-ethyl group. The N-benzyl grouping of (47) caused a multiplet at 2.7 (5H, aromatic protons) and a singlet at 6.32 (2H, benzylic protons).

Variation in the aldehyde used in the Mannich step was next investigated. After reduction and treatment with methylamine and benzaldehyde, m-dinitrobenzene gave a brown oily basic fraction, which was found to be a complex mixture. When benzaldehyde was replaced by acetaldehyde, the very small basic fraction, a dark gum, consisted mainly of one compound, but could not be solidified or

converted into a solid derivative.

Participation of the 1,3-dialdehyde glutaraldehyde in this reaction would theoretically be expected to result in the formation of the azatricyclododecane (51). In practice, however, use of a 25% aqueous solution of glutaraldehyde led to an almost insignificant basic fraction that was not further examined. Since the compound (2c) had been available in much higher yield than (1a), it was decided to employ methyl 3,5-dinitrobenzoate as starting material in an attempt to synthesise the tricyclic compound (52). The basic fraction isolated in this instance was however a complex mixture.

It could thus be seen that, not unexpectedly, only formaldehyde was sufficiently reactive to participate in this Mannich reaction.

By Michael condensation with electrophiles such as acrolein, acrylonitrile and phenyl vinyl ketone, the salts of type (53), obtainable
33
by reduction of the corresponding m-dinitrobenzenes, promised wide synthetic versatility in the preparations of carbocyclic 1,5-dinitro-bicyclo (3.3.1) non-2-enes, (Scheme I). Accordingly, suspensions of the salt (53, R=H) in the solvent mixture were treated at 0° with equimolar amounts of acrolein, with or without the addition of various bases (e.g., OH⁻, OEt⁻). After acidification, the dark oily products showed carbonyl absorption (indicating that some condensation had occurred), nitro, and hydroxyl absorption (perhaps due to cyclisation of the side chain). In the absence of base, considerable amounts of m-dinitrobenzene were recovered, together with two or three other compounds. Using base and

long reaction times, the products contained no m-dinitrobenzene, but were complex mixtures, distillation of which caused decomposition. Isolation of the salt (53, R=H) prior to addition of acrolein gave no purer products. The dry salt was also found to explode when touched. Similar results were encountered with acrylonitrile, viz., undistillable oils with IR nitrile, nitro and carbonyl absorptions, and containing several constituents.

Using phenyl vinyl ketone and the salt (53, R=H), (previously isolated and washed with dry ethanol) under a nitrogen atmosphere at a temperature of -70° , aliquots were removed from the reaction mixture after 5, 20, and 40 minutes and compared with the final product (isolated after 1 hr.). All had identical extremely complex thin layer chromatograms. IR spectroscopy indicated that condensation had occurred, since aromatic double bond and carbonyl, and nitro, bands were present. None of the products could however be obtained solid.

These experiments demonstrated convincingly that the salts (53) were of no synthetic value in the Michael reaction under these conditions.

By acidification of the disodium salts (53), Severin et al.³³ obtained dinitrocyclohexenes, e.g., 1-methyl-2,4-dinitrocyclohex-1-ene (54) from 2,4-dinitrotoluene. It was felt that Michael reactions, which were unsuccessful under the conditions described above, might proceed smoothly from these dinitrocyclohexenes in the presence of base.

Repetition of the published procedure for the preparation of (54) yielded after distillation a red oil exhibiting IR absorption at 1685 (C=C) and 1560 cm^{-1} (NO_2). It was however an unstable mixture of three compounds, two of which predominated (perhaps double bond isomers). On standing, $\nu_{\text{max}}^{\text{C=C}}$ was observed to diminish considerably.

Since the dinitrocyclohexene acid (55) was reported as a solid, m.p. 153°, by Severin³³, it was decided to attempt the preparation by a similar procedure of the isomeric acid (56) from the readily available 3,5-dinitrobenzoic acid. The red oily acidic fraction, shown by TLC analysis to be a single acid, decomposed on standing to material insoluble in ether. Also attempted was the synthesis of the ethyl ester (57) of (56). Ethyl 3,5-dinitrobenzoate afforded by similar means a dark red liquid, with IR ester, nitro and double bond absorption, but comprising several compounds.

Owing to the impurity and/or instability of these products, no condensations with electrophiles were attempted.

Mannich bis- condensations with formaldehyde and methylamine at sites activated by groups other than nitro, such as carbalkoxy, carboxy, and amido, are well known (see introduction). Examples of condensations with compounds possessing carbethoxy groups are the conversions of 2-carbethoxycyclohexanone, 2,5-dicarbethoxycyclohexanone and 2,4-dicarbethoxycyclopentanone to (58), (59) and (60) respectively.

It was planned to convert the readily available 2-carbethoxycyclohexanone to the compound (58), which on LAH reduction would afford the diol (61). Tosylation of (61) was anticipated to provide the monotosylate (62), oxidisable by Jones reagent to the ketotosylate (63). By analogy with other bicyclic ketotosylates, e.g., (64),⁶¹ base-catalysed bridge fission of (63) was expected to yield the azacyclooctane (65). A similar sequence from 2-carbethoxycyclopentanone via the ketoester (66) to the azacycloheptane (67) was also planned.

18,20

The literature procedure^{18,20} for the preparation of (58) gave a mixture of four compounds, from which reasonably pure (58) was isolated by preparative TLC in 15-21% overall yield. IR absorption occurred at 2790 (N-methyl), 1741 (ester C=O) and 1725 cm.⁻¹ (ketone C=O). The corresponding literature values²⁰ were 2770, 1730 and 1718 cm.⁻¹ respectively. The mass spectrum showed the correct molecular weight of 225, with peaks at 224 (loss of H), 196 (loss of Et) and 180 m/e (loss of OEt). Its NMR spectrum, which has not been reported, was very similar to that²⁴ of (59), (Table 25).

Under similar conditions, 2-carbethoxycyclopentanone furnished a much lower yield of basic material, which comprised four compounds. After separation by preparative TLC, examination of the two main components showed that neither was the desired ketoester (66).

Exposure of the ketoester (58) to excess LAH in refluxing THF provided 82% of the diol (61) as a viscous oil which slowly solidified.

Recrystallisation gave a colourless solid with a wide m.p. range, 105-131°. Both C₉ epimers were therefore probably present.

The m.p. could not be raised further, and satisfactory analysis figures were not obtained. Mass spectrometry however indicated the correct molecular weight of 185, and peaks at 184, 168 and 154 m/e corresponded to losses of H, OH and CH₂OH respectively. At this point, it was considered that spectroscopic characterisation of the diol (61) would be rendered more convincing by comparison with the available known diols (68), ⁶¹(69) and ^{61,62}(70). Their ⁶¹V_{OH}^{CCl₄} values are listed in Table 3. A sharp peak at ca. 3630 cm.⁻¹

was assigned to the free hydroxyl frequency, and broad, concentration independent absorption at 3540 cm.⁻¹ to the intramolecularly hydrogen-bonded hydroxyl frequency. In the NMR spectra (Table 26), the hydroxyl protons gave rise to a broad singlet in the region 6.9-7.8, the bridge carbonyl proton to signals of different types at ca. 6.3, and the other carbonyl protons to either a singlet or a doublet at ca. 6.6. In the case of (61), a singlet at 7.89 (3H) was attributed to the N-methyl protons.

When treated with tosyl chloride in pyridine at 0°, the diols (68), (69), (70) and (61) formed the monotosylates (71), (72), (73) and (62) in yields of 99, 64, ca. 73 and 10% respectively.

In the cases of (71) and (72), preparative TLC was employed to separate the C₁₀ and C₉ epimeric pairs respectively. Reasonably pure (62), a brown oil, was obtained also by preparative TLC. The IR spectra of the monotosylates (Table 9) exhibited peaks at ca. 3630 (free OH), 3570 (broad, concentration independent absorption, (intramolecularly bonded OH), 1370, 1192, 1180 (S=O), and 1600, 1500 cm.⁻¹ (aromatic C=C). Similarities were also observed in their NMR spectra (Table 27). The tosyloxymethyl group was responsible for a pair of doublets at ca. 2.0 and 2.5 (4H, each J ca. 9c/s, aromatic protons), an AB quartet in the region 6.0-6.4 (2H, J=9-10c/s, non-equivalent methylene protons) and a singlet at 7.48-7.58 (3H, aromatic methyl protons). The single bridge carbonyl proton resonated as a singlet at ca. 6.3.

An epimeric mixture of the monotosylate (72) has been reported⁶² as having m.p. 65-67°. In the present work, the less polar epimer was found to have m.p. 71-72°, and to analyse correctly for C₁₈H₂₄O₄S. The other epimer was an oil which could not be induced to solidify. Similar behaviour was exhibited by the two epimers of (71), the less polar having m.p. 130-137°. The monotosylate (73) analysed correctly for C₁₉H₂₈O₄S.

Jones oxidation of the less polar epimer of the monotosylate (71) afforded a mixture of two compounds. The less polar of these, obtainable in 57% yield after preparative TLC, had m.p. 82.5-83.5°,

and analysed for the ketotosylate (74), $C_{19}H_{24}O_4S$. The other constituent, present in much smaller amounts, was also a crystalline solid, and was shown by IR and NMR spectroscopy to possess the tosyloxymethyl group, but to lack a double bond or a carbonyl group. This material was not further examined, nor was the oxidation product of the more polar epimer of (71), which constituted a complex mixture containing some acidic material.

The ketotosylate (75), $C_{18}H_{22}O_4S$, was formed by oxidation of either epimer of the monotosylate (72). Repeated running of the TLC chromatogram of (75) revealed the presence of two compounds with nearly identical R_f values. These were considered to be Δ^2 double bond isomers, formed in the acidic oxidation conditions.

The ketotosylate (76) was available in almost quantitative yield from the monotosylate (73). It had the expected molecular weight of 350 (mass spectrum). Major peaks in the mass spectrum were at 195 (loss of Ts), 179 (loss of OTs) and 178 (loss of HOTs) m/e.

The ketotosylate (63) could not be obtained in a satisfactory state of purity, despite the use of preparative TLC. It was a brown gum which did not solidify.

Table 10 shows the absence of IR hydroxyl peaks, and the retention of bands due to S=O and aromatic C=C, similar to those described above for the diol-monotosylates. The bicyclo (4.3.1) decanes (74) and (76) had $\nu_{\text{max}}^{C=O}$ 1708 and 1709 cm^{-1} respectively,

and the bicyclo (3.3.1) nonanes (63) and (75) had $\nu_{\text{max}}^{\text{C=O}}$ 1715 and 1718 cm^{-1} respectively. The NMR spectra (Table 28) demonstrated the absence of the bridge carbinyl proton. The only other difference compared with the spectra of the diol-monotosylates was that the methylene protons of the tosyloxymethyl group, with the exception of those of (76), no longer resonated as an AB quartet in the region 6.0-6.4, but as a singlet in the region 5.8-6.0. It was therefore concluded that in the absence of the constraint imposed by the intramolecular hydrogen bond in the diol-monotosylates, the tosyloxymethyl group of the ketotosylates was free to rotate, resulting in equivalence of the two methylene protons. This transformation from non-equivalence to equivalence was manifested by replacement of the AB quartet by a singlet.

Now that the four ketotosylates were available, the action of strong base on them could be examined. However, since the ketotosylate (63) was not obtainable pure, it was decided to investigate only the behaviour of (74), (75), and (76) under basic conditions.

On prolonged reflux with ethanolic ethoxide, the ketotosylate (76) was partially converted into two other compounds. The more polar of these products had $\nu_{\text{max}}^{\text{CCl}_4}$ at 3630 (free OH), 3515 (concentration independent peak, intramolecularly bonded OH), and a doublet at 1696, 1686 cm^{-1} (carbonyl). These data suggested the presence of the ketol (77), a possible mode of formation of which is outlined in Scheme J.

The twin carbonyl was explicable on the basis of a hydrogen-bonded (1686 cm.^{-1}) and a non-hydrogen-bonded (1696 cm.^{-1}) carbonyl group. Treatment of the more polar product with tosyl chloride in pyridine effected partial conversion to a less polar compound with a R_f value identical to that of the ketotosylate (76). This confirmed the formation of (77).

The ketotosylate (75), after subjection to a four day reflux with ethanolic ethoxide, afforded a mixture containing unchanged starting material. IR absorption at 3500 (hydroxyl) and 1710 cm.^{-1} (carbonyl) however suggested the presence in the mixture of the ketol (78).

With *t*-butoxide in *t*-butanol, (76) was converted completely into a mixture of four compounds. Since the IR spectrum of the product was similar to that of the ketol (77), it was probable that the most polar constituent was (77).

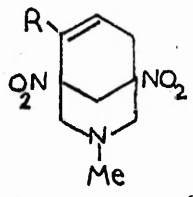
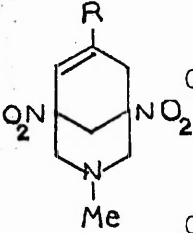
Similar IR absorption was exhibited by the products from (74) and (75), and it again seemed likely that one constituent of each of these mixtures was (79) and (78) respectively.

None of the products from these attempted bridge fission reactions was observed to have IR peaks due to an ester carbonyl or an exomethylene group.

The remarkable resistance to bridge fission exhibited by the compounds (74), (75) and (76) necessitated some explanation.

Examination of models of these ketotosylates showed that the tosyloxymethyl group was free to rotate, a fact which was mentioned when the NMR spectra of these compounds were discussed (vide supra). Hence in only one position (80) is the $\text{CH}_2\text{-OTs}$ bond in the required trans and coplanar relationship with the bond linking the bridge carbonyl with the carbon atom carrying the tosyloxymethyl group. Any other position e.g., (81), of the $\text{CH}_2\text{-OTs}$ bond would be expected to prevent bridge fission and concomitant elimination of tosylate anion. In ketotosylates, e.g., (64), reported^{61,62} to undergo bridge-fission, the two bonds cleaved were fixed antiparallel to each other.

Table 1 Absorption frequencies in CCl_4 of some 6- and 7-substituted 1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)non-6-enes

	R	NMe	C=C	NO ₂ str.		absorption due to R
				asym.	sym.	
	H	2790	3048(=C-H) 795,752 ^b	1547	1354,1338	
	Me	2802		1553	1343	
	Cl	2802	1665	1562 1552	1368,1343	
	OMe	2804	1680	1561 1553	1345	1245(=C-O)
	CO ₂ Et	2804	1660	1560 1554sh	1361,1348	1734sh,1723(C=O) 1262(C-O)
	CO ₂ H ^a		1655	1560 1546	1356,1344	2260-2760 ^c (NH ⁺ ionised aminoacid ^e) 1708(C=O)
	CO ₂ H ^a		1657	1555	1349	2330-2630 ^d (NH ⁺ ionised aminoacid ^e) 1703(C=O)
	CONH ₂ ^a	2808	1659	1551	1352	3458(free NH),3170 (bonded NH),1696 (amide I C=O),1618 (amide II C=O)
	CO ₂ Et	2800	1660	1553	1368,1341	1724(C=O),1272, 1261(C-O)
	CO ₂ Me	2798	1661	1555	1368,1341	1729(C=O),1274, 1262(C-O)
	OMe	2800	1669 790,740 ^f	1552	1369,1342	1235(=C-O)

a. nujol mull

b. CS₂ solution

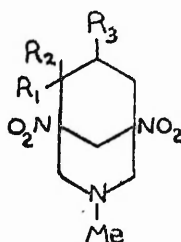
c. broad absorption, with peaks at 2700, 2635, and 2570 cm.⁻¹

d. broad absorption

e. Nakanishi, Infra-red Absorption Spectroscopy, p. 39.

f. thin film

Table 2 Absorption frequencies in nujol of some 6- and 7-substituted 1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)nonanes

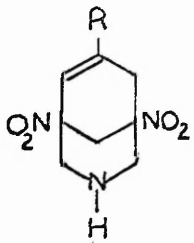
	R ₁	R ₂	R ₃	NMe	NO ₂ asym.	str. sym.	absorption due to R
	H	H	H ^a	2797	1562	1345	
	H	OH	OH	2808	1551	1356	3487sharp(free OH)
						1348	3310broad(bonded OH)
	Me	OH	OH	2813	1549	1351	3515, 3495
					1538		
	Me	H	OH	2808	1551	1354	3623
	H	H	OH ^b	2822	1551	1342	3450-ca. 3100 ^c

a. CCl₄ solution

b. CHCl₃ solution

c. broad absorption, unaffected by dilution, i.e., intramolecular hydrogen bonding

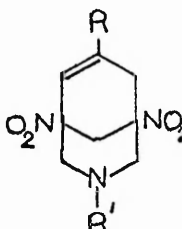
Table 3 Absorption frequencies in nujol of some 7-substituted-3-azabicyclo(3.3.1)non-6-enes

	R	NH	C=C	NO ₂ asym.	str. sym.	absorption due to R
	H			1562	1358	
	CONH ₂	3525	1652	1560sh 1551	1348	3458, 3410(free amide NH), 3190broad(bonded amide NH), 1680(amide I C=O), 1602(amide II C=O)
	CO ₂ Me		1664	1568 1556	1346	1736(C=O), 1276, 1250(C-O)
	OMe ^a	3400 ^b	1663	1550	1366 1339	1236(=C-O)

a. CHCl₃ solution


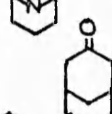

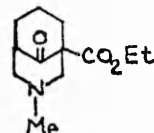


b. liquid film

Table 4 Absorption frequencies in CCl_4 of some 3-substituted and 7-substituted 1,5-dinitro-3-azabicyclo(3.3.1)non-6-enes

	R	R'	C=C str.	NO ₂ str. asym. sym.	absorption due to R
	H	Et		1555 1353	
	H	CH_2Ph^a		1553 1358	3060, 3030(ar.=C-H str.) 1606, 1498(ar.C=C str.) 748, 706(ar.=C-H def.)
	OMe	Et	3097(=C-H)	1553 1370 1340	1233(=C-O)
	OMe	CH_2Ph	3091(=C-H) 1670	1554 1371 1342	3070, 3030(ar.=C-H str.) 1497(ar.C=C) 1232(=C-O)

a. thin film

Table 5 Comparison of the carbonyl stretching frequency of the aminoketone (23) with those of cyclohexanone and several bicyclic ketones

ketone	$\nu_{\text{C=O}}$ in CCl_4	$\nu_{\text{C=O}}$ in CHCl_3
cyclohexanone	1717 ^a	
aminoketone (23) ^f	1734	1727
 (29)	1729 ^b	
 (32)	1709 ^c	
 (30)	1717, 1706 ^a	
 (58)	1733 ^d 1730, 1710 ^{sh} ^e 1724 ^g	1710 ^e
 (58)	1730(ester) ^g 1741 -- 1725(ketone) ^f 1718 -- ^g	
 (58)	1725 ^h	

- a. Zbinden and Hall, J. Amer. Chem. Soc., 1960, 82, 1215.
 b. Eglinton, Martin, and Parker, J. Chem. Soc., 1965, 1243.
 c. Leonard, Morrow, and Rogers, J. Amer. Chem. Soc., 1957, 79, 5476.
 d. Reference 9. e. Reference 17. f. present study. g. Reference 20
 h. O.S. Foote, Ph.D. Dissertation, Harvard University, 1961.

Table 6 Absorption frequencies in CHCl_3 of some 3-substituted-1,5-dinitro-3-azabicyclo(3.3.1)nonan-7-ones

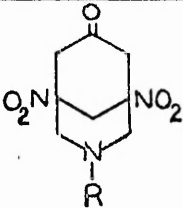
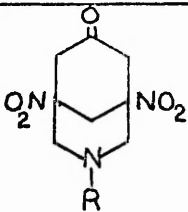
	R	NO_2 str.		absorption due to R
		asym.	sym.	
	Me	1551	1369	2808
	Et	1553	1370	
	CH_2Ph	1552	1372	3035(ar.=C-H) 1495(ar.C=C)
	H	1553	1361	3400(N-H)

Table 7 Carbonyl stretching absorption frequencies of some 3-substituted-1,5-dinitro-3-azabicyclo(3.3.1)nonan-7-ones

	R	CCl_4	CHCl_3
	Me	1734	1727
	Et	1732	1727
	CH_2Ph	1731	1727
	H		1735 ^a

a. centre of broad band

Table 8 Hydroxyl stretching absorption frequencies in CCl_4 of some bicyclic 1,3-diols

compound	free OH str.	bonded OH str. ^b
diol (61) ^a	3635	3535
diol (68)	3635	3540
diol (69) ^c	3620	3500
diol (70)	3640	3580

a. C-H str. of NCH_3 at 2780 cm^{-1}

b. broad absorption, unchanged by dilution, i.e., intramolecular hydrogen bonding

c. CHCl_3 solution

Table 9 Absorption frequencies in CCl_4 of some bicyclic diol 1,3-monotosylates

compound	OH str.		S=O str.	C=C
	free OH	bonded CH ^b		
monotosylate (62) ^a	3620 ^c	3560, 3475 ^{c,e}	1360, 1192, 1180 ^d	1601, 1496 ^d (ar.C=C)
monotosylate (71)	3635 ^f 3640 ^f	3560 ^c 3565 ^f	1370, 1192, 1180	3015(=C-H) 1498(ar.C=C)
monotosylate (72) ^g	3640	3575	1370, 1192, 1180	3025(=C-H) 1602, 1499 (ar.C=C)
monotosylate (73)	3640	3580 ^e	1380, 1372, 1192 1181	1601, 1497 (ar.C=C)

a. C-H str. of NCH_3 at 2780 cm^{-1} (CHCl_3)

b. as above

c. as above

d. thin film

e. approximate values only, since absorption is very much broader than the other cases

f. more polar epimer; other absorptions were identical to the less polar epimer

g. less polar epimer

Table 10 Absorption frequencies in CCl_4 of some bicyclic 1-keto-3-tosylates

compound	C=O str.	S=O str.	C=C
ketotosylate (63) ^a	1715 ^b	1370, 1190, 1180	1600, 1495(ar.C=C str.)
ketotosylate (74)	1708	1372, 1190, 1179	3020(=C-H str.), 1600, 1496(ar.C=C str.)
ketotosylate (75)	1718	1374, 1191, 1180	3025(=C-H str.), 1601, 1498(ar.C=C str.)
ketotosylate (76)	1709	1374, 1191, 1180	1600, 1496(ar.C=C str.)

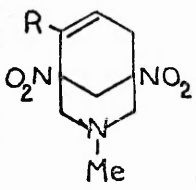
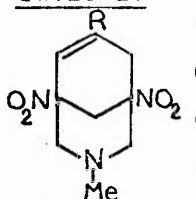
a. less exact values, recorded on a thin film; also, C-H str. of NCH_3 at 2780 cm^{-1}

b. CHCl_3 solution; also, absorption of unknown origin at 1667 cm^{-1}

Tables 11, 12, and 13

Mass spectra of some 6-substituted (Table 11) and 7-substituted (Table 12) 1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)non-6-enes, and of some 1,5-dinitro-3-azabicyclo(3.3.1)nonanes (Table 13)

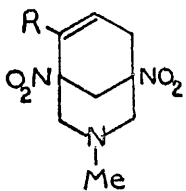
Table 11^a

compound	R	mol.wt.	l o s s e s						others
			NO (30)	NO ₂ (46)	HNO ₂ (47)	2NO (60)	2NO ₂ (92)	HNO ₂ ¹ +NO ₂ (93) ²	
	H	227		181	180	167	135	134	
	CH ₃	241	211	195	194	181	149	148	
	Cl	261	231	215	214	201	169	168	
		263	233	217	216	203	171	170	
	OMe	257	227	211	210	197	165	164	243(CH ₃)
	CO ₂ H	271		225	224	211	179	178	254(OH) 226(CO ₂ H)
	CO ₂ Et	299		253	252		207	206	254(OEt)
	CO ₂ H	271	241	225	224	211	179	178	254(OH) ^b
	CO ₂ Et	299	269	253	252	239	207	206	254(OEt)
	CO ₂ Me	285	255	239	238	225	193	192	254(OMe)
	CONH ₂	270	240	224	223	210	178	177	
Table 13									
olefin (34)		241	211	195	194	181	149	148	226(CH ₃) 91(possibly C ₇ H ₇ ⁺)
amine (12)		229	199	183	182	169	137	136	
diol (15)		261		215			169	168	244(OH) 243(H ₂ O)

a. common to all the spectra in these tables was a peak at 91^{m/e}.
(possibly C₇H₇⁺)

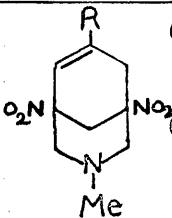
b. also a peak at 226 (loss of CO₂H)

Table 14 NMR spectral assignments of some 6-substituted-1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)non-6-enes in CDCl_3

type of proton							
R	olefinic	allylic	bridge	NCH_2	NCH_3	others	
	$\text{H}^{\text{a,c}}$	3.89s	7.20broad s	6.75 ^d J=11c/s	7.4-7.7 ^b complex	7.57s	
	CH_3	4.27m half-band width 7c/s	7.24m half-band width 8c/s	6.60 ^e 6.79	ca.7.6 ^b 7.70s	7.58s	8.36d J=2c/s methyl
	Cl^{c}	3.86t J=4c/s	7.10d J=4c/s	6.59 ^e 6.77	7.39 ^e 7.60	7.53s	
	OMe	5.13t J=4c/s	7.15d J=4c/s	6.60 ^e 6.78	7.50 ^b 7.70 broad s	7.58s	6.45s methoxyl
	CO_2Et	2.85t J=4c/s	7.03d J=4c/s	6.58 ^e 6.75	7.24s 7.40s	7.59s	5.79q, 8.73t both J=7c/s ethyl ester

- Table 18 compares the signals of this compound in CDCl_3 , C_6D_6 , and $\text{CF}_3\text{CO}_2\text{H}$
- partially obscured by the NCH_3 resonance
- picrate showed no shift in signals
- apparent triplet
- both broad singlets
- the bridge protons of these compounds all had this J value

Table 15 NMR spectral assignments of some 7-substituted-1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)non-6-enes in CDCl_3

type of proton							
R	olefinic	allylic	bridge	NCH_2	NCH_3	others	
	$\text{CO}_2\text{Et}^{\text{a}}$	2.83 ^e 6c/s ^d	7.01 ^e 6c/s ^d	6.77 ^b J=11c/s	7.26 ^c 7.40	7.61s	5.73q, 8.67t both J=7c/s ethyl ester
	CO_2Me	2.80 ^e 6c/s ^d	6.96 ^e 6c/s ^d	6.72 ^b J=10.5c/s	7.24 ^c 7.39	7.61s	6.17s methyl ester
	OMe	5.00 ^e 4c/s ^d	7.24 ^e 4c/s ^d	6.85 ^b J=12c/s	7.4-7.7 ^f complex	7.62s	6.43s methoxyl

- picrate showed no shift in signals
- apparent triplet
- both broad singlets
- half-band width value
- broad singlet
- partially obscured by NCH_3 resonance

Table 16 NMR spectral assignments of some 3-substituted-1,5-dinitro-3-azabicyclo(3.3.1)non-6-enes in CDCl_3

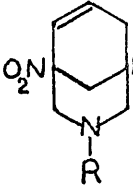
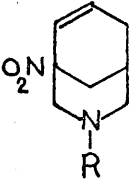
		t y p e o f p r o t o n				
	R	olefinic	allylic	bridge	NCH_2	NR
	Me	3.89s	7.20 ^e	6.75 ^d J=11c/s	7.4-7.7 ^a complex	7.57s
	Et	3.98s	7.26 ^{b,e}	6.73 ^d J=11c/s	7.44s 7.62s ^b	ca.7.4q,8.94t both J=7.5c/s
	CH_2Ph^c	3.95s	7.26 ^e	6.73 ^d J=10c/s	7.36s 7.54s	2.72s(aromatic H) 6.28s(benzylic H)

Table 17 NMR spectral assignments of some 3-substituted-1,5-dinitro-3-azabicyclo(3.3.1)non-6-enes in $\text{CF}_3\text{CO}_2\text{H}$

		t y p e o f p r o t o n		
	R	olefinic	NCH_2	NR
	H	2.46d J=6c/s	6.37 ^e	1.65s
	Me	3.75d J=6c/s	6.79 ^e	6.68s
	Et	3.70d J=6c/s	6.78 ^e	6.28q,8.43t both J=7c/s

a. partially obscured by the NCH_3 resonance

b. overlapped by the NET quartet

c. spectrum of picrate (other signals at 0.84s (2H, picrate anion H), 3.2m (1H, NH^+)) f. speculative assignment

d. apparent triplet g. C_6 proton signal (J=2.3c/s) } superimposed on a

e. broad singlet h. C_7 proton signal (J=3c/s) } broad multiplet

Table 18 NMR spectral assignments of 1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)non-6-ene (1a) in CDCl_3 , C_6D_6 , and $\text{CF}_3\text{CO}_2\text{H}$

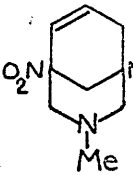
	solvent	olefinic	allylic	bridge	NCH_2	NCH_3
	CDCl_3	3.89s	7.20 ^e	6.75 ^d J=11c/s	7.4-7.7 ^a complex	7.57s
	C_6D_6	4.43d ^g 4.67t ^h			7.90 ^{e,f} 8.2 ^{a,f}	8.28s
	$\text{CF}_3\text{CO}_2\text{H}$	3.75d J=6c/s			6.79 ^e	6.68s

Table 19 NMR shifts^a (in ppm relative to the parent amine) of protons attached to carbon atoms α and β ^b to nitrogen in amine picrates^c

	$\Delta(\alpha\text{CH}_2)$	$\Delta(\beta\text{CH})$
triethylamine	0.75	0.33
tri-n-butylamine	0.78	0.21
diethylamine	0.54	0.24
di-n-butylamine	0.52	0.14 ^d
piperidine	0.48	0.23

a. solvent CDCl_3

b. shifts for protons on δC were negligible

c. picrates of primary amines, e.g., cyclohexylamine, n-propylamine, and n-butylamine, and of some secondary amines, e.g., morpholine, were too insoluble in CDCl_3

d. approximate, since signal due to βCH was a broad multiplet

Table 20 Comparison of the NMR shifts (in ppm relative to triethylamine) of triethylamine picrate and hydrochloride in CDCl_3 and D_2O

	$\Delta(\alpha\text{CH}_2)$		$\Delta(\beta\text{CH})$	
	CDCl_3	D_2O	CDCl_3	D_2O
picrate	0.75	0.65	0.33	0.28
hydrochloride	0.64	0.67	0.38	0.28

Table 21 NMR spectral assignments of some 1,5-dinitro-3-azabicyclo(3.3.1)nonenes in $\text{CF}_3\text{CO}_2\text{H}$

	t y p e o f p r o t o n			
	olefinic	NCH_2	NR	others
diol (15)			6.71s	
vinyl ether (2e)	4.88s	6.84 ^b	6.70s	6.29s (methoxyl)
acid (1e)	2.31t J=4c/s	6.5-6.9 complex	6.66s	
acid (2a)	2.55 ^b 4c/s ^a	6.52 ^c 6.79	6.67s	
ethyl ester (2b)	2.65 ^b 6c/s ^a	6.50 ^c 6.81	6.67s	5.51q, 8.55t both J=7c/s(ethyl)
methyl ester (2c)	2.73 ^b 4c/s ^a	6.58 ^c 6.85	6.72s	6.03s (methyl)
methyl ester (39)	2.75 ^b 5c/s ^a	6.58 ^b 6.7-6.9 complex	1.64s	6.02s (methyl)
amide (2d)	2.84 ^b 5c/s ^a	6.46 ^c 6.78	6.65s	ca.2.4, broad absorption (amide H)
amide (42)	2.92 ^b 6c/s ^a	6.50 ^c 6.78	1.60d J=5.5c/s	2.42, broad absorption (amide H)

a. half-band width value

b. broad singlet

c. both broad singlets

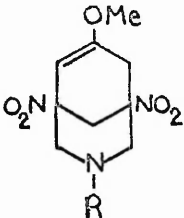
Table 22 NMR spectral assignments of some 1,5-dinitro-3-methyl-3-azabicyclo(3.3.1)nonanes in CDCl_3

	t y p e o f p r o t o n			
	bridge	NCH_2	NCH_3	others
amine (12)	6.47, 6.67 ⁿ	7.43s	7.66s	
diol (19)	6.60 ⁱ	7.56 ^a 7.73 broad s	7.64s	5.45m ^b (C_7 carbinyll H) 7.27s, 8.41s (hydroxyl H) 8.58s (methyl H)
alcohol (26)	6.65q J=11c/s	7.5-7.9 ^a complex	7.65s	5.45m ^d (C_7 carbinyll H) 8.95d (J=6c/s, methyl H)
alcohol (33)	6.52 ^h 6.62	7.42 ^a	7.49s	2.9d ^{c,e} (J=12c/s, hydroxyl H) 5.80m ^f (C_7 carbinyll H) 7.63d ^g (J=3c/s, C_6 and C_8 H)

a-i. see next page

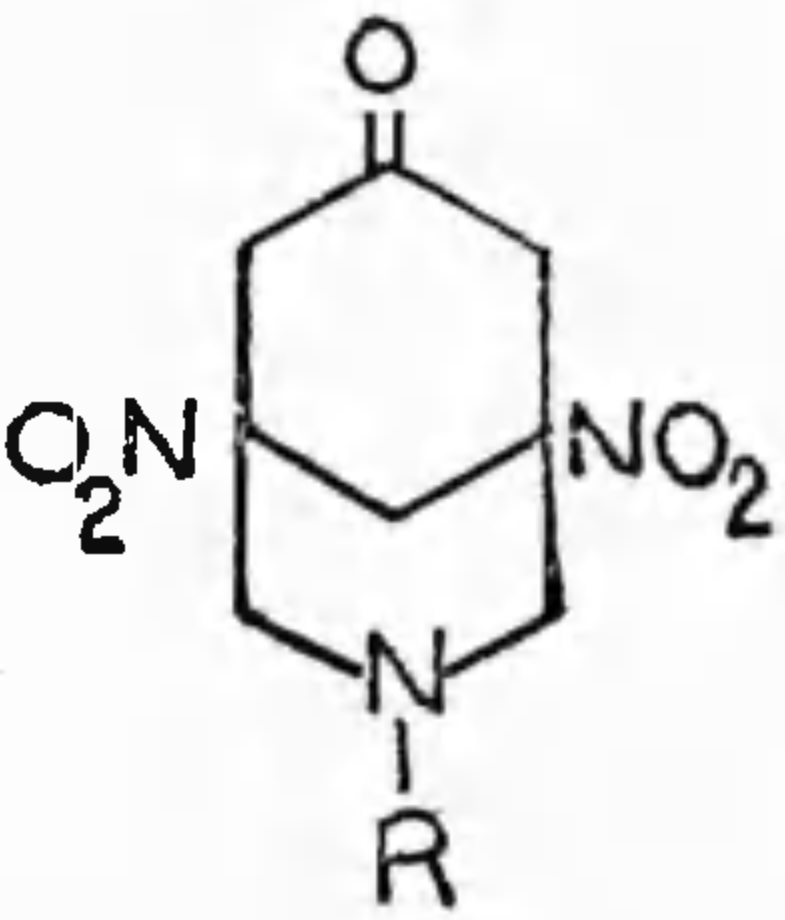
- a. partially obscured by the NCH_3 resonance
- b. centre of very broad multiplet (J_{base} ca.25c/s); half-band width value indicated equatorial (exo) hydroxyl (see discussion)
- c. signals disappeared on adding D_2O
- d. centre of very broad multiplet (J_{base} ca.30c/s); half-band width value indicated equatorial (exo) hydroxyl (see discussion)
- e. doublet caused by the hydroxyl H not being exchanged, i.e., constrained by the N atom (see discussion)
- f. half-band width value of 11c/s meant that hydroxyl group was axial (endo) (see discussion)
- g. J value pointed to an equatorial C_7 carbonyl H (see discussion)
- h. apparent pair of very slightly split doublets, but probably an AB quartet with $J=12\text{c/s}$
- i. apparent triplet with $J=12\text{c/s}$

Table 23 NMR spectral assignments of some 3-substituted-1,5-dinitro-7-methoxy-5-azabicyclo(3.3.1)non-6-enes in CDCl_3

	R	type of proton					
		olefinic	allylic	bridge	NCH_3	NR	methoxyl
	H	4.93 ^a 3c/s ^d	7.17 ^a 4c/s ^d	6.71 ^c	6.87s 6.95s	7.93s	6.36s
	Me	5.00 ^a 4c/s ^d	7.24 ^a 4c/s ^d	6.85 ^c	7.4-7.7 complex	7.62s	6.45s
	Et	4.98 ^a 4c/s ^d	7.25 ^{a,b}	6.77 ^c	7.4-7.7 ^b complex	7.37q 8.94t $J=7\text{c/s}$	6.40s
	CH_2Ph	4.96 ^a ca.6c/s ^d	7.25 ^a 4c/s ^d	6.82 ^c	7.3-7.6 complex	2.74s (ar.H) 6.31s (benzylic H)	6.38s

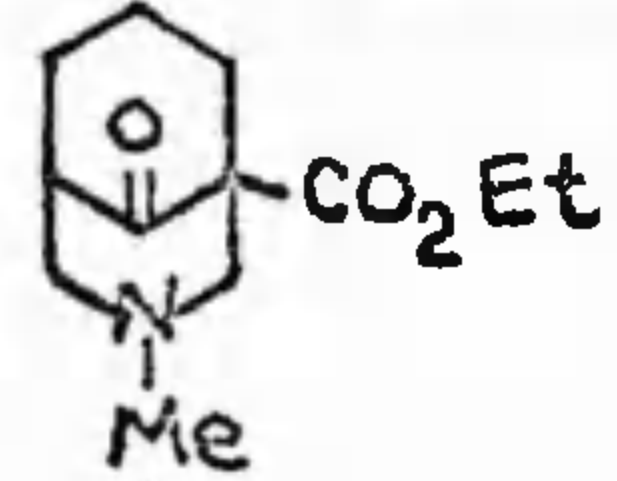
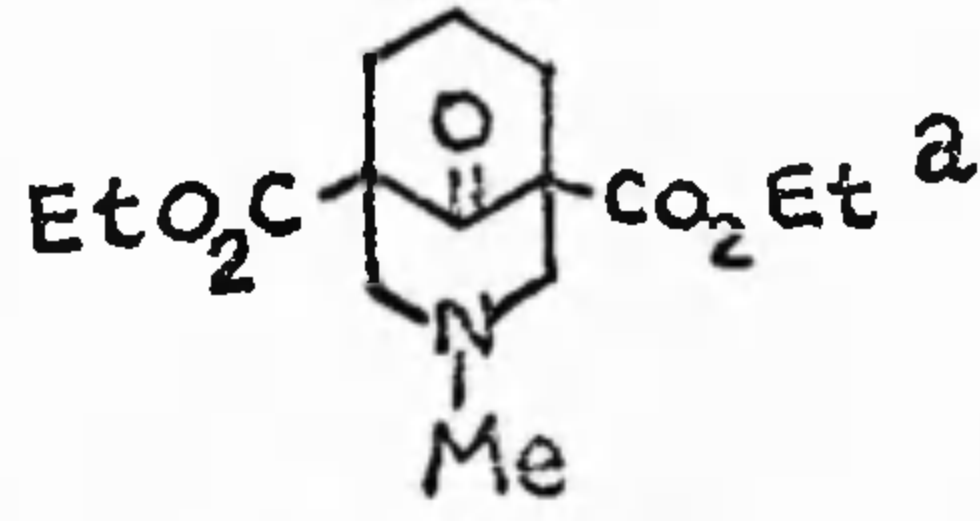
- a. broad singlet
- b. partially obscured by the quartet at 7.37 τ
- c. apparent triplet, $J=11-12\text{c/s}$
- d. half-band width value

Table 24 NMR spectral assignments of some 3-substituted-1,5-dinitro-3-azabicyclo(3.3.1)nonan-7-ones in CDCl_3

t y p e o f p r o t o n					
	R	C_6 and C_8	bridge	NCH_2	NR
	Me	7.04s	6.85 ^a	7.21s, 7.40s	7.59s
	Et	7.09s	6.82 ^a	7.18s, 7.37s	7.36q, 8.97t both $J=7\text{c/s}$
	CH_2Ph	7.10s	6.83 ^a	7.24s, 7.43s	2.7m($J_{\text{base}}^{30\text{c/s}}$, aromatic H) 6.52s(benzylic H)

a. apparent triplet ($J=11\text{c/s}$), with highest field signal obscured by CH_2CO resonance

Table 25 Comparison of the NMR spectra of 1-carbethoxy-3-methyl-3-azabicyclo(3.3.1)nonan-9-one and its 1,5-dicarbethoxy analogue in CDCl_3

t y p e o f p r o t o n				
	ethoxyl CH_2	NCH_2	NCH_3	ethoxyl CH_3
	5.77q $J=7\text{c/s}$	6.92m	7.72s	8.72t $J=7\text{c/s}$
	5.78q $J=7\text{c/s}$	6.89s	7.65s	8.72t $J=7\text{c/s}$

a. reference 24

Table 26 NMR spectral assignments of some bicyclic 1,3-diols in CDCl_3

t y p e o f p r o t o n				
	hydroxyl	carbinyl	ring methylene	others
diol (61)	6.93 ^a broad s	6.34m(half-band width 11c/s, C_9H) 6.57d($J=6\text{c/s}$) ^d	7.1-8.8 complex	7.89s(NCH_3)
diol (68)	6.90 ^a broad s	6.24 ^b broad s ^c 6.53d($J=3\text{c/s}$) ^d	7.7-8.8 complex	4.56m(olefinic H) 8.97s(methyl)
diol (69)	7.28m ^a	6.39s(C_9H) 6.55s ^d	7.9-8.8 complex	4.3m, 4.8m(olefinic H), 8.99s(methyl)
diol (70)	7.8 ^a broad s	6.02d ^c ($J=8.5\text{c/s}$) 6.72s ^d	7.6-8.9 complex	8.96s(methyl)

- a. signal disappeared in D₂O
- b. sharpened on D₂O exchange
- c. C₁₀ H signal
- d. CH₂OH signal

Table 27 NMR spectral assignments of some bicyclic diol 1,3-monotosylates in CDCl₃

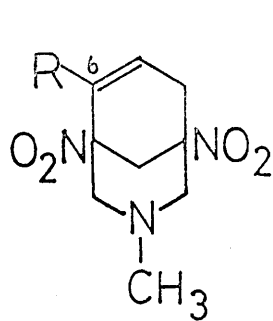
t y p e o f p r o t o n				
	hydroxyl	carbinyll CH ₂ OTs	aromatic	aromatic others methyl
monotosylate (62)	6.36s	6.23q J=9c/s	2.15d ^a 2.61d J=8.5c/s	7.56s 6.9-7.5(NCH ₃) ² 7.89s(NCH ₃)
monotosylate (71) ^c	8.10s ^d	6.20s	5.98q J=10c/s	1.90d ^a 2.40d J=9c/s
monotosylate (72) ^c		ca.6.3 ^b	6.03q J=10c/s	1.91d ^a 2.40d J=9c/s
monotosylate (73)		b	6.35q J=9c/s	2.18d ^a 2.63d J=8.5c/s
				7.48s 4.40broad s (olefinic) 8.93s(methyl)
				7.48s 4.15m, 4.65m (olefinic) 8.97s(methyl)
				7.58s

- a. due to two aromatic H adjacent to O; other doublet caused by the other two aromatic H
- b. obscured by the CH₂OTs quartet
- c. less polar epimer
- d. signal disappeared in D₂O

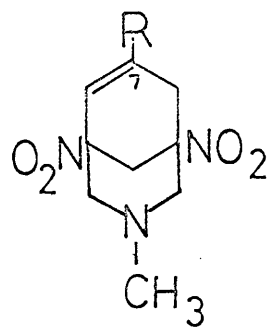
Table 28 NMR spectral assignments of some bicyclic 1-keto-3-tosylates in CDCl₃

t y p e o f p r o t o n				
	CH ₂ OTs	aromatic	ar.methyl	others
ketotosylate (63)	6.01broad s	2.23d ^a 2.68d J=8.5c/s	7.57s	7.91s(NCH ₃)
ketotosylate (74)	5.83s	1.90d ^a 2.39d J=9c/s	7.48s	4.0-4.3m(olefinic H) 7.65d(J=3.5c/s, C ₉ H) 8.92s(methyl)
ketotosylate (75)	5.85s	1.90d ^a 2.39d J=9c/s	7.48s	3.95m, 4.55m(olefinic H), 8.92s(methyl)
ketotosylate (76)	6.13q J=9c/s	2.23d ^a 2.63d J=8.5c/s	7.57s	

a. as above



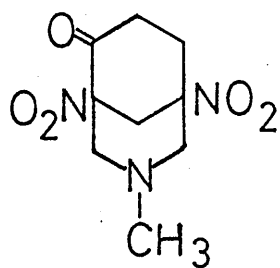
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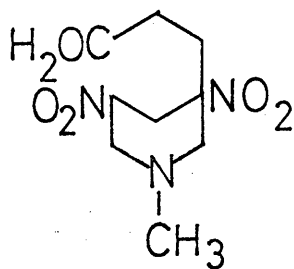
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- a $R = H$
- b $R = CH_3$
- c $R = Cl$
- d $R = OCH_3$
- e $R = CO_2H$
- f $R = CO_2Et$

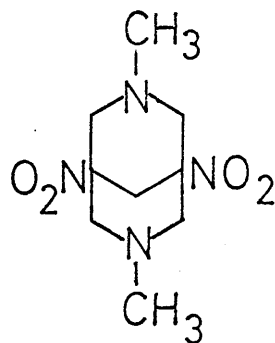
- a $R = CO_2H$
- b $R = CO_2Et$
- c $R = CO_2Me$
- d $R = CONH_2$
- e $R = OCH_3$



3

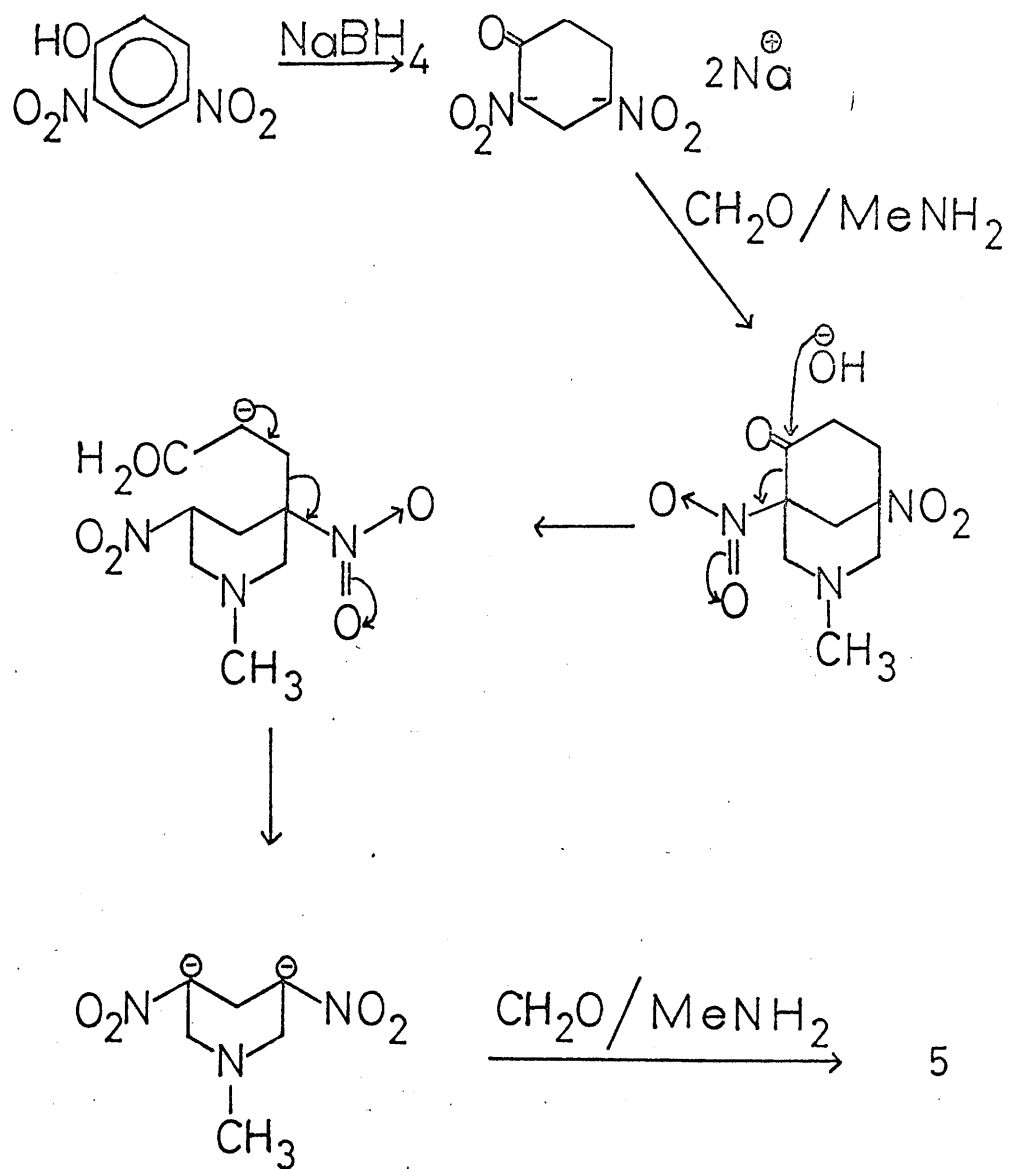


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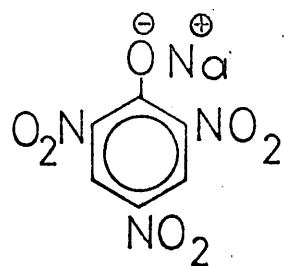


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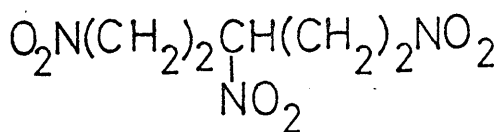
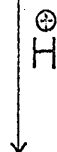
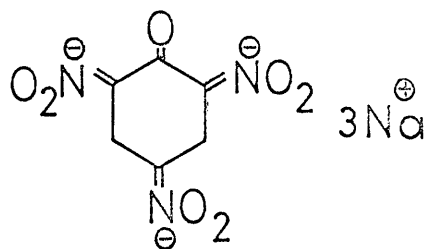
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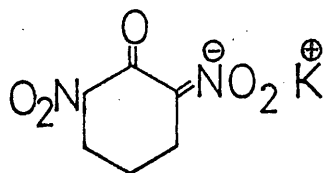
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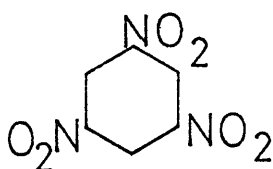
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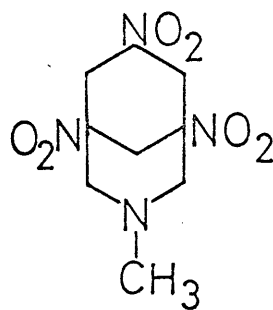
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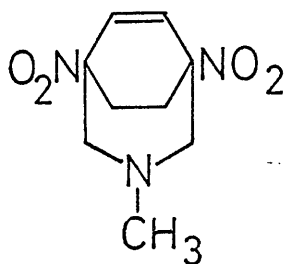
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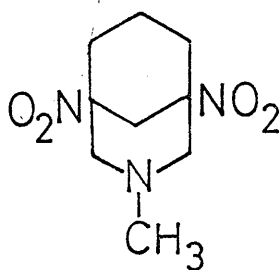
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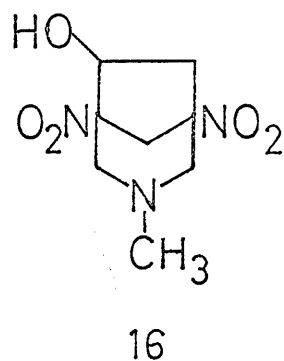
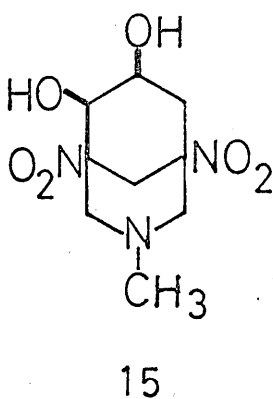
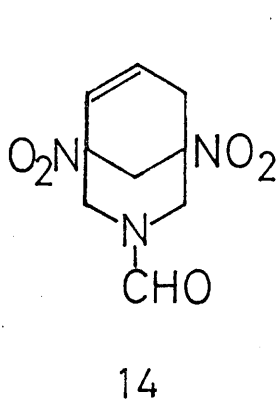
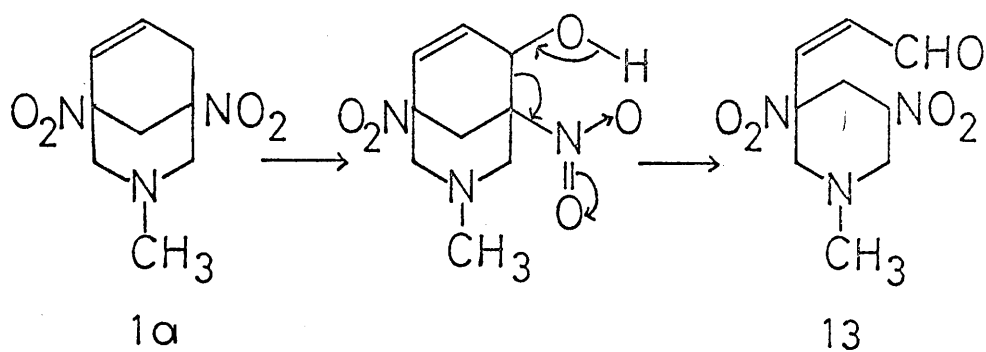


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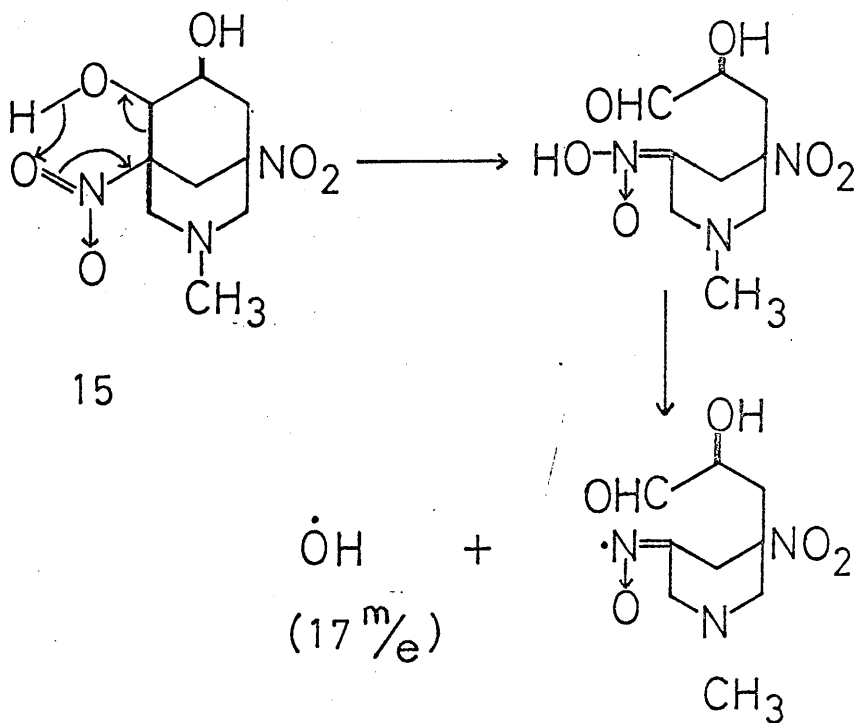


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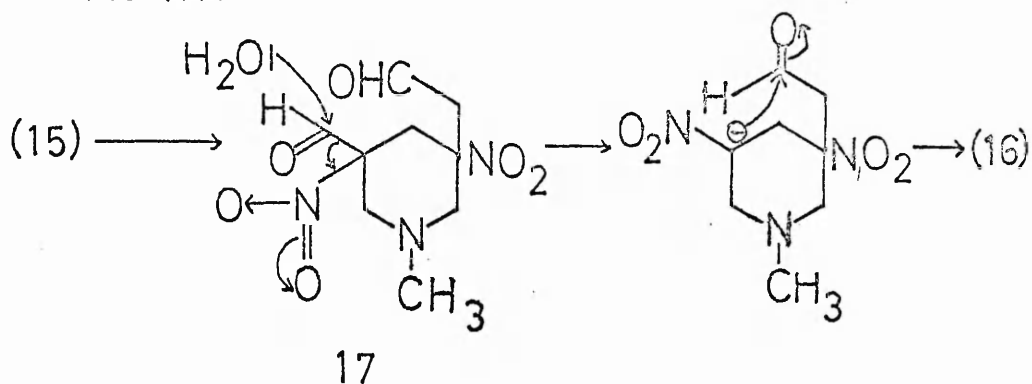
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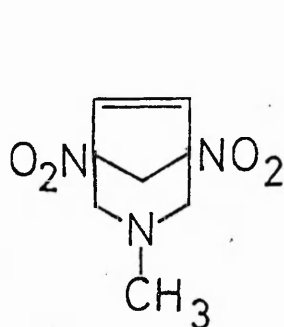
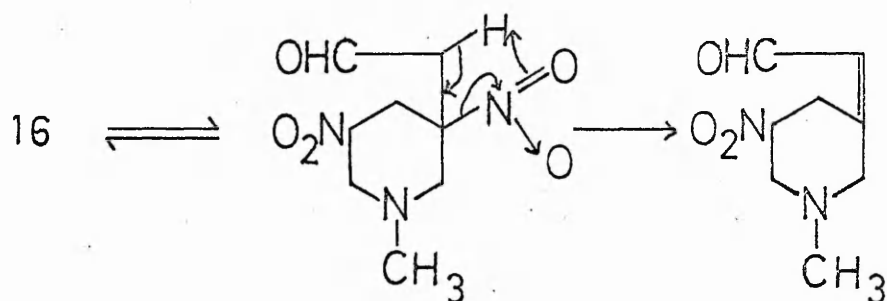
SCHEME D



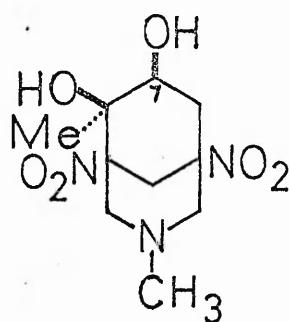
SCHEME E



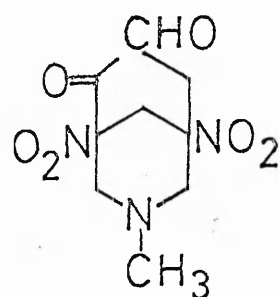
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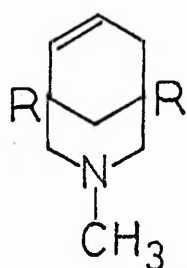
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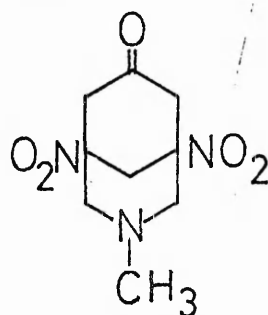
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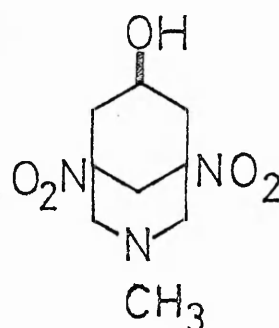
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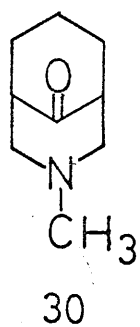
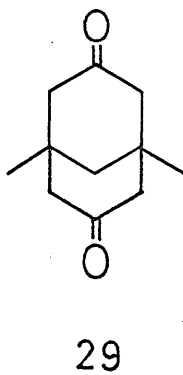
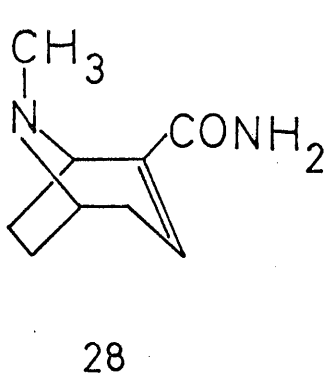
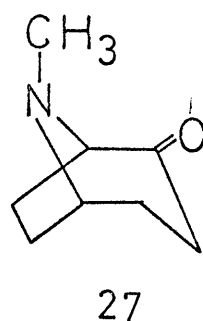
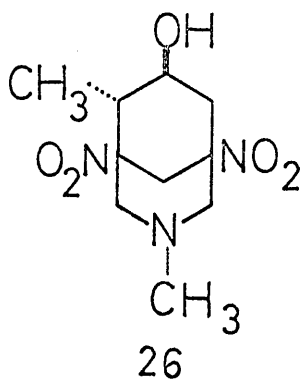
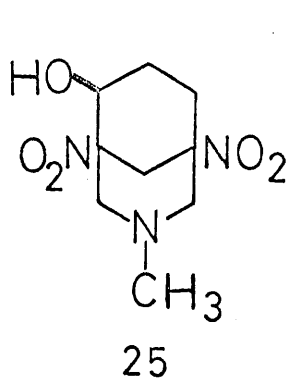
21 R = NH₂
22 R = OAc



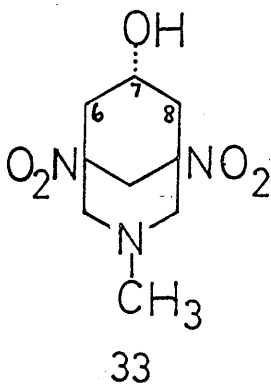
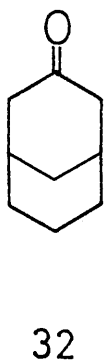
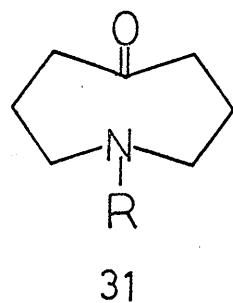
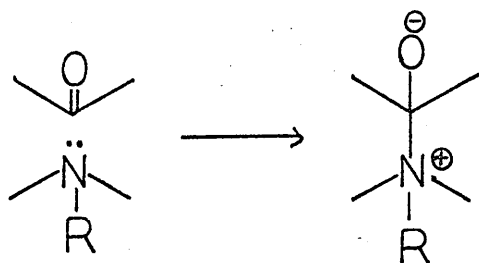
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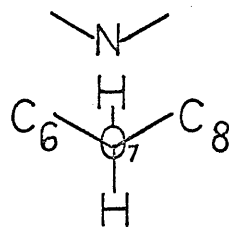
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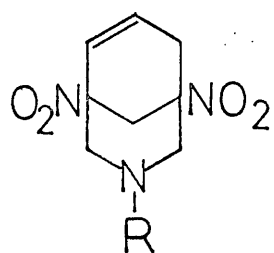


SCHEME G



SCHEME H





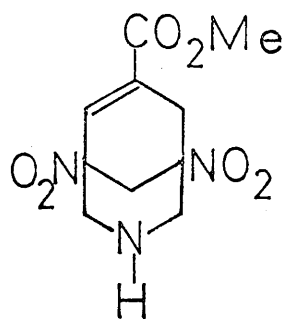
34 R=Et

35 R=CH₂Ph

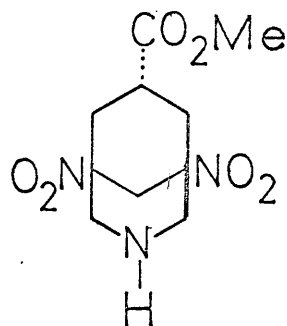
36 R=H

37 R=Ph

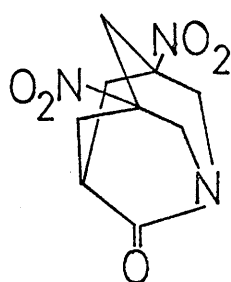
38 R=COCH₃



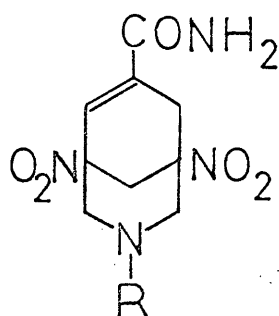
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40



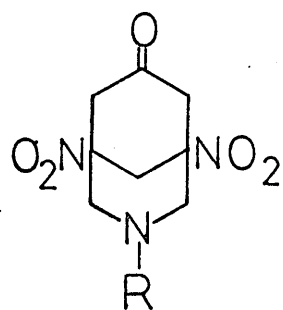
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42 R=H

43 R=Et

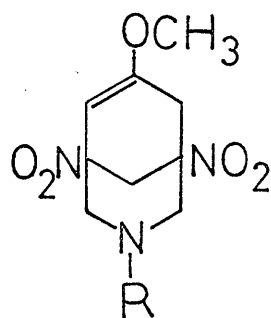
44 R=CH₂Ph



45 R=H

46 R=Et

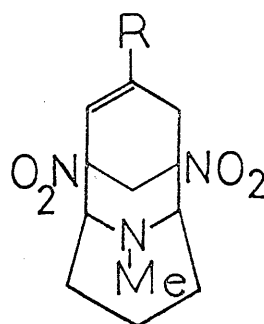
47 R=CH₂Ph



48 R=H

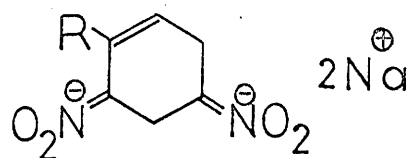
49 R=Et

50 R=CH₂Ph

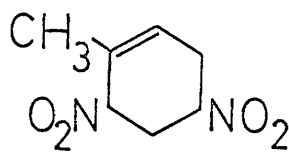


51 R=H

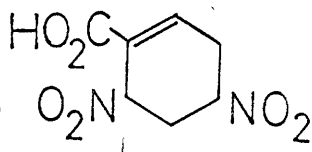
52 R=CO₂Me



53

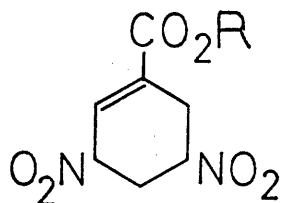
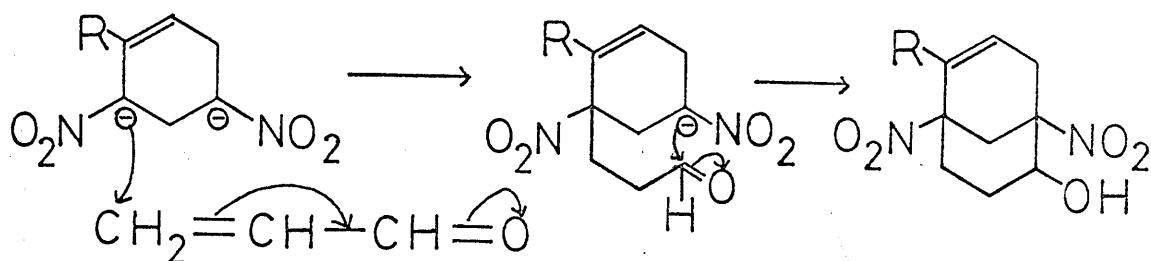


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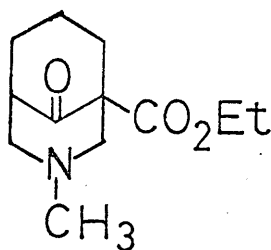
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SCHEME I

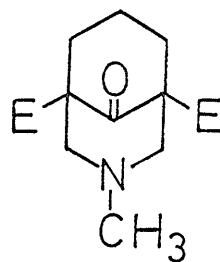


56 R = H

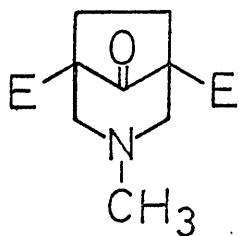
57 R = Et



58

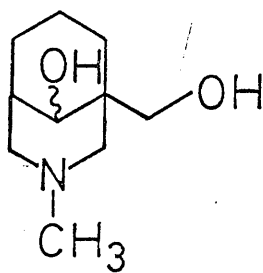


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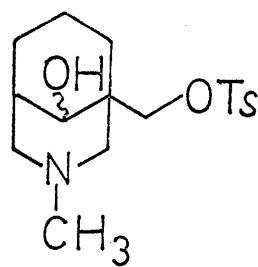


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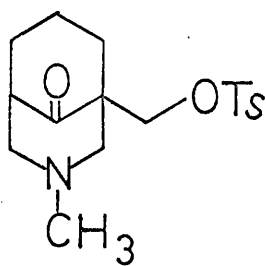
E = CO₂Et



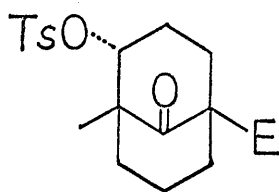
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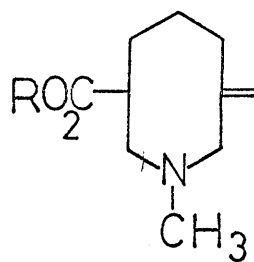
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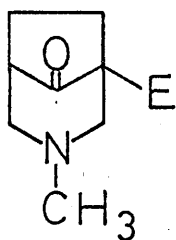
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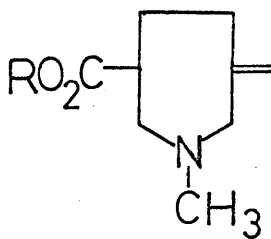
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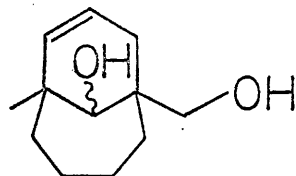
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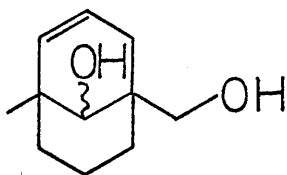
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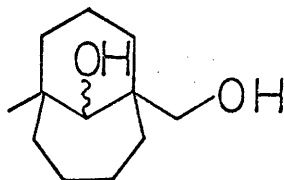
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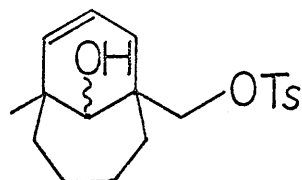
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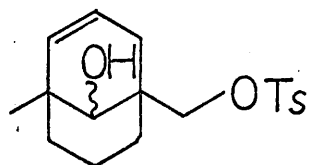
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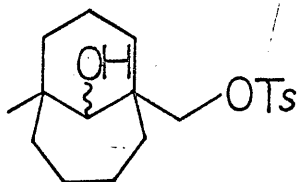
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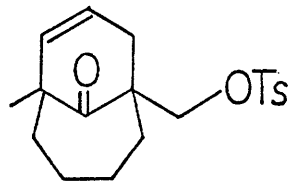
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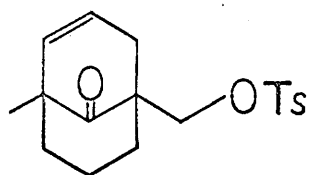
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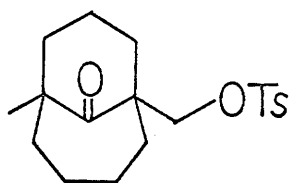
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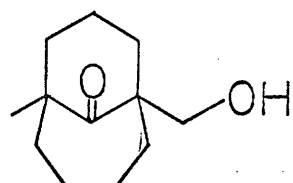
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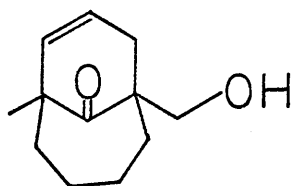
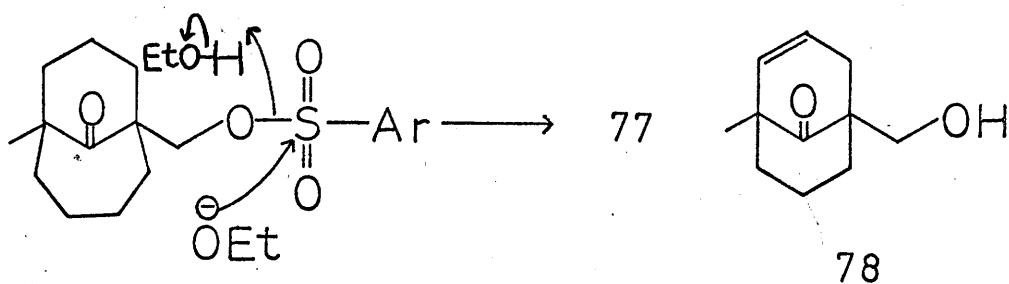


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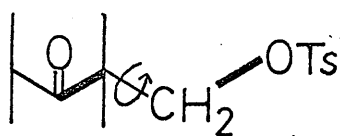


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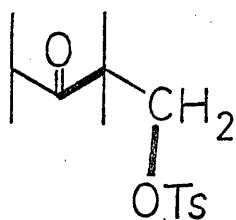
SCHEME J



79



80



81

EXPERIMENTAL

General literature procedure for reaction of dinitrobenzenes with sodium borohydride, formaldehyde, and amine³⁵.

The dinitrobenzene compound in a suitable solvent mixture was treated portionwise with solid sodium borohydride with stirring and cooling (temperature best kept in the range 5-18°). The end of the reaction (15-30 min. for 4 gm. of compound) was indicated by a change in the initial dark blue colour to yellow or light brown. (The salt-like intermediate can be precipitated by isopropanol and redissolved in water). The mixture was diluted with water, cooled, and a cooled mixture of amine, water, and formaldehyde was added. Immediate acidification with acetic acid, extraction with methylene chloride, washing of organic extracts with water, drying (over CaCl_2), and removal of solvents left a residue purified by recrystallisation or occasionally by chromatography on neutral alumina with methylene chloride.

Amendments were made to the above procedure, e.g., organic extracts were washed always with brine, and dried always with MgSO_4 . The occasions when the reaction was stirred for various periods before and after acidification, or when chloroform was used for extraction, are mentioned individually.

The formaldehyde and methylamine used were in the form of 40% and 25% aqueous solutions respectively.

35

1,5-dinitro-3-methyl-3-azabicyclo (3.3.1)non-6-ene (1a)

From m-dinitrobenzene (7 gm.) was obtained a red oil (after overnight stirring of the reaction mixture), which slowly crystallised. Recrystallisation from methanol, then ethanol, gave (1a) as a pale yellow crystalline solid (4.34 gm.; 46%; Lit. 79%). Colourless material, m.p. 76° (Lit. 75°) was obtained by many recrystallisations from ethanol (incurring heavy loss). Light petroleum 60-80° was later found to be a more efficient recrystallising solvent.

IR, table 1; NMR, table 14; mass spectrum, table 11.

35

1,5-dinitro-3,6-dimethyl-3-azabicyclo (3.3.1) non-6-ene (1b)

2,4-dinitrotoluene (4 gm.) formed (after overnight stirring of the reaction mixture) a red oil, which became a yellow solid after rubbing with a spatula. Recrystallisation from isopropanol (Lit.) was effective only initially, but recrystallisation from ethanol gave (1b) as a pale yellow solid (2.04 gm.; 36%; Lit. 58%), m.p. 97° (Lit. 98°).

IR, table 1; NMR, table 14; mass spectrum, table 11.

35

1,5-dinitro-3-methyl-6-chloro-3-azabicyclo (3.3.1)non-6-ene (1c)

2,4-dinitrochlorobenzene (4 gm.) afforded (on stirring the reaction mixture for 3 hr.) a red oil, which crystallised rapidly on cooling. Yield of orange crystals (2X isopropanol) 2.97 gm. (58%; Lit. 44%, after chromatography on alumina with methylene chloride). Further recrystallisations (1X isopropanol, 3X ethanol) gave (1c) as colourless crystals, m.p. 113-114° (Lit. 114°).

IR, table 1; NMR, table 14; mass spectrum, table 11.

1,5-dinitro-3-methyl-6-methoxy-3-azabicyclo (3.3.1)non-6-ene (1d)

2,4-dinitroanisole (2 gm.; prepared from 2,4-dinitro-
chlorobenzene ³⁸) dissolved in THF (10 ml.), formamide (20 ml.) and
methanol (10 ml.), treated under conditions described in the
preparation of (2c), formed a red oil (2.33 gm.), rapidly solidifying
on standing. This was extracted with hot ethanol, cooled, and
filtered to remove precipitated black tar. The filtrate was
cooled (ice-salt bath) yielding successive crops of (1d) as an
off-white crystalline solid (765 mg.; 30%). Further recrystal-
lisation from ethanol (large wastage) gave colourless needles, m.p.
140.5 - 141.5°.

Found: C, 46.54 ; H, 5.54 ; N, 16.04. $C_{10}H_{15}N_3O_5$ requires
C, 46.69; H, 5.88; N, 16.33.

IR, table 1; NMR, table 14; mass spectrum, table 11.

Hydrolysis of (1d)

The vinyl ether (1d), (5 mg.), was heated for 30 min.
on the steam bath with (a) dilute hydrochloric acid (6N; 1 ml.) and
water (1 ml.), and (b) concentrated hydrochloric acid (2 ml.), the
solution turning pale yellow, then basified in both cases with
saturated sodium carbonate solution. Only starting material
(IR, TLC) was recovered from (a). No product was obtained from
(b), indicating that water-soluble material had been formed.

1,5-dinitro-3-methyl-6-carboxy-3-azabicyclo (3.3.1)non-6-ene (1e)

Application of the procedure used in the preparation of (2a), to 2,4-dinitrobenzoic acid (4 gm.; prepared from 2,4-dinitrotoluene³⁹) furnished (1e) as a pale yellow solid (560 mg.; 11%), m.p. 224-226°, after recrystallisation from ethanol (considerable wastage). The aminoacid was only slightly soluble in water, but soluble in both dilute acid and base.

Found: C, 44.29; H, 4.54; N, 15.45. $C_{10}H_{13}N_3O_6$ requires C, 44.28; H, 4.83; N, 15.49.

IR, table 1; NMR, table 21; mass spectrum, table 11.

1,5-dinitro-3-methyl-6-carbethoxy-3-azabicyclo (3.3.1)non-6-ene (1f)

Under the conditions described for the preparation of (2b), ethyl 2,4-dinitrobenzoate (2 gm.) afforded a red oil (2.03 gm.) which did not solidify, had no N-methyl absorption in the IR, and appeared to consist of two main components (TLC). The product was dissolved in chloroform, and washed with saturated sodium bicarbonate solution, and dilute hydrochloric acid. The acidic fraction was a complex mixture (TLC), as were also the neutrals (constituting most of the material), whereas the basic fraction (which slowly solidified) was a single compound (TLC). Yield 101 mg. (4%), m.p. 133-134.5°, after recrystallisation from ethanol.

Found: C, 47.77; H, 5.44; N, 13.99. $C_{12}H_{17}N_3O_6$ requires C, 48.16; H, 5.73; N, 14.04.

IR, table1; NMR, table14; mass spectrum, table11.

1,5-dinitro-3-methyl-7-carboxy-3-azabicyclo(3.3.1) non-6-ene (2a)

To a stirred solution of 3,5-dinitrobenzoic acid (4 gm.) and sodium hydroxide (0.9 gm.) in water (40 ml.), was added a solution of sodium borohydride (0.2 gm.) in water (2 ml.). After the initially violent reaction (dark red colour produced) had subsided, a solution of sodium borohydride (1.8 gm.) in water (8 ml.) was added, and the mixture stirred for 30 min. Dilution with ice-water (50 ml.) was followed by addition of a mixture of 15 ml. each of formaldehyde, methylamine, and water. Stirring was continued for 30 min., the mixture acidified with acetic acid (15 ml.), and stirred for 1 hr. The usual extraction procedure afforded (2a) as a pale yellow crystalline solid (560 mg.; 11%). The yield was not increased by a 3 day constant ethyl acetate extraction. Recrystallisation from ethanol gave colourless crystalline material, m.p. 185-186.5°.

Found: C, 44.48 ; H, 5.07 ; N, 15.57. $C_{10}H_{13}N_3O_6$ requires C, 44.28; H, 4.83; N, 15.49.

IR, table1; NMR, table21; mass spectrum, table12.

1,5-dinitro-3-methyl-7-carbethoxy-3-azabicyclo(3.3.1)non-6-ene (2b)

Ethyl 3,5-dinitrobenzoate (2 gm.) dissolved in THF (15 ml.) and ethanol (15 ml.), was reduced by sodium borohydride (1.5 gm.). Then were added ice-water (50 ml.), the usual mixture (7.5 ml. of

each constituent), and acetic acid (7.5 ml.). After being stirred for 17 hr., extraction gave (2b) as pale yellow crystalline material (2.45 gm.; 98%). Colourless feathery crystals, m.p. 101-102°, were obtained by recrystallisation from ethanol. Found: C, 48.15; H, 5.40; N, 13.84. $C_{12}H_{17}N_3O_6$ requires C, 48.16; H, 5.73; N, 14.04. IR, table 1; NMR, table 15; mass spectrum, table 12.

Esterification of (2a) to (2b)

The aminoacid (2a), (50 mg.), was heated for 18 hr. with ethanol (3 ml.) and dilute sulphuric acid (6 ml.), cooled, basified with aqueous sodium carbonate, and extracted with chloroform. The organic extracts were washed, dried, and evaporated, leaving a yellow oil which contained mainly (2b), together with a more polar component (TLC). Separation by preparative TLC (eluant: light petroleum/20% EtOAc) yielded the less polar component as a yellow oil solidifying on standing (6mg.; 11%), identical (IR, TLC) to (2b) obtained above.

1,5-dinitro-3-methyl-7-carbomethoxy-3-azabicyclo (3.3.1)non-6-ene (2c)

From methyl 3,5-dinitrobenzoate (2 gm.), following the procedure used in the preparation of (2b), (2c) was obtained as a red oil which crystallised on cooling (2.47 gm.; 98%), m.p. 122-124° (colourless plates from ethanol).

Found: C, 46.28; H, 5.40; N, 14.71. $C_{11}H_{15}N_3O_6$ requires
C, 46.32; H, 5.30; N, 14.73.

IR, table 1; NMR, table 15; mass spectrum, table 12.

1,5-dinitro-3,7-dimethyl-3,7-diazabicyclo (3.3.1)nonane (5)

2,4-dinitrophenol (10 gm.) in THF (25 ml.), formamide (50 ml.), and ethanol (62.5 ml.) was reduced by sodium borohydride (7.5 gm.). Ice-water (250 ml.), followed by a mixture of 37.5 ml. each of formaldehyde, methylamine and water, and finally acetic acid (37.5 ml.) were added. After being stirred for 3 hr., extraction gave a dark-red oil (4.10 gm.), which became a black semi-solid tar on standing. Several purifications (as for (1c)) yielded a pale yellow crystalline solid (164 mg.; 1.2%), which became colourless needles, m.p. 117-118°, on further recrystallisation from ethanol.

Found: C, 44.34; H, 6.59; N, 20.95. $C_7H_{16}N_4O_4$ requires
C, 44.26; H, 6.60; N, 22.94.

Mass spectrum ($P=244$ m/e) contained peaks at 243 (P-1), 198 (P-46, loss of NO_2) and 151 (P-93, loss of NO_2 and HNO_2) m/e.

NMR($CDCl_3$): 7.13 q ($J=11$ c/s, bridge H) and 7.34s (10H in all, NCH_2); 7.64s (6H, NCH_3). IR (CCl_4): 2812, 2798, 1551 and 1353 cm^{-1}

1,3,5-trinitrocyclohexane (9)³²

A solution of trinitrobenzene (2 gm.) in THF (10 ml.) was added slowly dropwise to a cooled solution of sodium borohydride

(2 gm.) in water (25 ml.) and methanol (25 ml.). The dark-red solution was stirred for 30 min., acidified with 10% aqueous tartaric acid (90 ml.) and filtered. Extraction gave a dark-red oil, which decomposed rapidly on standing to form material insoluble in chloroform. The product was extracted with chloroform to yield a more mobile red oil which did not solidify (560 mg.; 28%; Lit. recrystallised from isopropanol, m.p. 125°, 40%). It consisted mainly of one compound (TLC). IR (CHCl_3) 1563 cm^{-1} (NO_2 asym. str.).

Attempted preparation of 1,5,7-trinitro-3-methyl-3-azabicyclo(3.3.1)nonane (10)

Trinitrobenzene (2 gm.), reduced as in the preparation of (9), yielded, under conditions described in the preparation of (2), a red oil (1.56 gm.). Acid extraction of the product gave a basic brown oil, which appeared to be mainly one very crude compound (TLC), exhibiting hydroxyl, nitro, and N-methyl absorption in the IR. It could not be obtained solid. Treatment with an ethanolic solution of picric acid gave a yellow precipitate, which when filtered, quickly became a brown gum.

Attempted preparation of 1,5-dinitro-3-methyl-3-azabicyclo (3.2.2.) non-6-ene (11).

p-Dinitrobenzene (390 mg.; prepared from p-nitroaniline)⁴⁰ was dissolved in ethanol (3 ml.) and THF (9 ml.), and treated with sodium borohydride (0.4 gm.). No signs of reaction (cf, effervescence

observed for m-dinitro compounds) were noticed, and the initial pale yellow colour became orange-pink and cloudy (NaBH_4 in suspension). The usual procedure (see preparation of (2b)) gave after two hours' stirring a clear red solution, from which basic material was extracted as a pale brown oil (75 mg.). The product was a mixture of three compounds (TLC), and the main constituent (separated by preparative TLC), with an R_f value similar to that of (1a), did not have IR or NMR absorption expected for (11).

1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) nonane (12)

The olefin (1a), (227 mg.; 1mM), in ethyl acetate (15 ml.) was hydrogenated for 4 hr. with 10% palladium on charcoal (100 mg.).

Filtration, and evaporation of solvent gave a viscous pale yellow oil (188 mg.). TLC analysis showed the presence of unchanged (1a), a less polar compound, and a more polar one. Separation by preparative TLC (thickness 1 mm., eluant: light petroleum/20% EtOAc) yielded:-

i) most polar material (92 mg.), a mixture of possibly three components (TLC), with strong N-H absorption in the IR.

ii) starting olefin (6 mg.)

iii) least polar material, a pale yellow oil which solidified

(85 mg.; 37%). Recrystallisation from light petroleum 60-80° gave (12) as colourless crystalline material, m.p. 66-69°.

IR, table 2; NMR, table 22; mass spectrum, table 13.

Selenium dioxide oxidation of olefin (1a)

The olefin (1a), (6.84 gm.; 0.03M), in water (500 ml.) was refluxed for 18 hr. with selenium dioxide (6.72 gm.; 0.06M). The red selenium formed was filtered, and the filtrate (acid to indicator paper) extracted with chloroform (6 X). The organic extract was washed, dried, and evaporated, leaving a viscous dark-red oil (1.15 gm.). The yield was not improved by either a constant ethyl acetate extraction of the aqueous layer, or a chloroform extraction of the aqueous layer after basification with saturated sodium bicarbonate solution or saturated sodium hydroxide solution. The product consisted mainly of one compound, and three less polar ones (TLC). Occasionally, the oil could be purified by crystallisation from carbon tetrachloride, but usually purification was accomplished by preparative TLC (thickness 0.8 mm., eluant: light petroleum/60% EtOAc). The main compound, an orange oil (530 mg.), solidified, m.p. 64-68°, after distillation, becoming colourless needles, m.p. 68-69°, on recrystallisation from carbon tetrachloride.

Found: C, 50.51; H, 6.20; N, 12.55. $C_9H_{14}N_2O_4$ (214) requires C, 50.46; H, 6.59; N, 13.08. Mass spectrum (P apparently = 242 m/e, but no losses of, e.g., 30 (NO), or 46 (NO₂) were observed). Also, two spectra of later products, although identical up to 170 m/e, continued to different m/e values. IR (CHCl₃) 1702, 1551 cm.⁻¹

NMR (CDCl₃) 0.37s (1H, aldehyde H); 3.62d (2H, J=6.5c/s, olefinic H

on cis C=C); 6.10 q (2H, J= 12 c/s, bridge H); 6.89 s (4H) and 7.13 broad s (4H) could not be assigned. UV $\lambda_{\text{Max}}^{\text{EtOH}}$ 227 m μ (e3600). Although soluble in dilute hydrochloric acid, no picrate could be prepared. Fehling's and silver mirror tests were both positive.

1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) nonan-6,7-diol (15)

The aminoolefin (12), (885 mg.; 3.9 mM), in a solution of osmium tetroxide (1 gm.; 3.94 mM) in dry pyridine⁵⁰ (15 ml.) was left for two days at room temperature. A solution of sodium bisulphite (1.8 gm.) in water (30 ml.) and pyridine (20 ml.) was then added. The mixture was stirred for one hour, extracted with chloroform (3 X), and the organic extracts washed, dried, and evaporated, leaving (15) as a yellow crystalline solid (944 mg.; 93%). Several recrystallisations from aqueous ethanol gave a colourless crystalline solid, m.p. ca. 128-144°. The narrowest m.p. range observed was 150-153° (a sample recrystallised 3 X aqueous EtOH).

Found: C, 41.40; H, 5.49; N, 15.90. C₉H₁₅N₃O₆ requires C, 41.38; H, 5.79; N, 16.09.

IR, table 2; NMR, table 21; mass spectrum, table 13.

1,5-dinitro-3-methyl-3-azabicyclo (3.2.1) octan-6-ol (16)

a) from diol (15)

To the diol (15), (522 mg.; 2mM), dissolved in methanol (50 ml.) was added sodium metaperiodate (530 mg.). After being

stirred under nitrogen for 18 hr., brine was added, and the mixture extracted with chloroform. The organic extract was washed, dried, and evaporated under reduced pressure without heating (the product was unstable to heat), leaving a brown oil which slowly solidified. Its IR spectrum showed hydroxyl, N-methyl, nitro and carbonyl (1720 cm^{-1}) absorption. It contained mainly one compound, less polar than the starting diol, and an even less polar component (TLC). (A product with no carbonyl absorption in the IR, and consisting only of the more polar compound, was obtained by repeating the experiment with a stirring time of 60 hr.). The product was purified by dissolving in a little cold benzene, cooling in an ice-salt bath, adding a large volume of carbon tetrachloride, followed by light petroleum 40-60°, and filtering. Two such recrystallisations gave (16) as a pale brown crystalline solid (219 mg.; 47%), m.p. 96-99°. Alternatively, preparative TLC (thickness 1 mm., eluant: light petroleum/30% EtOAc) yielded identical material from the more polar band.

The alcohol decomposed slowly on standing by elimination of nitrous acid (odour detectable), and a satisfactorily pure analytical sample could not be obtained. Mass spectrum ($P=231\text{ m/e}$) showed peaks at 230 (P-1), 214 (P-17, loss of OH), 185 (P-46, loss of NO_2), 184 (P-47, loss of HNO_2), 139 (P-92, loss of 2NO_2), and 138 (P-93, loss of NO_2 and HNO_2) m/e .

IR (CHCl_3) 3595 sharp (free OH), 2805, 1549, 1371 cm^{-1} NMR (CDCl_3) 5.5 m (1H, half-band width 12 c/s, $\text{C}_6\text{-H}$); 6.73t (2H, $J=10\text{c/s}$, bridge H); 7.42, ca. 7.6 (NCH_2), and 7.59s (10H in all, NCH_3); hydroxyl and $\text{C}_7\text{-H}$ not assignable.

b) from diol (19)

A solution of diol (19), (138 mg.; 0.5 mM), in methanol (10 ml.) was stirred under nitrogen with sodium metaperiodate (130 mg.) for 15 hr. Extraction as in (a) furnished a yellow oil (120 mg.) containing some starting diol (present even in a reaction mixture stirred for 2 days), and a less polar compound (TLC). The IR spectrum again showed carbonyl absorption. Preparative TLC (as for (a)) afforded material identical to that obtained from diol (15), (IR, TLC).

Attempted tosylation of (16)

A mixture containing (16), (47 mg.; 0.2 mM), dry pyridine (1.5 ml.) and tosyl chloride (40 mg.; 0.2 mM) was kept at 0° for 16 days, and then poured onto ice and extracted with chloroform (3 X). The chloroform extract was washed, dried, and evaporated (pyridine removed by azeotropic distillation with dry benzene). The product consisted almost entirely of unchanged (16), (IR as for (16)), with weak tosylate peaks at 1600 cm^{-1} and in the fingerprint region; TLC showed only (16)).

Attempted Jones oxidation of (16)

A solution of (16), (23 mg.; 0.1 mM), in acetone (5 ml.)

was treated with excess Jones reagent. Chloroform extraction yielded an oil which solidified (18 mg.). It contained only (16), (TLC), with a trace of ketone (IR, 1710 cm^{-1} v.w.; remainder of spectrum identical to that of (16)).

1,5-dinitro-3,6-dimethyl-3-azabicyclo (3.3.1)nonan-6,7-diol (19)

Hydroxylation of the aminoolefin (1b), (470 mg.; 1.95 mM) with osmium tetroxide (0.5 gm.; 1.97 mM), in the same way as in the preparation of (15), furnished (19) as a viscous yellow oil (535 mg.; 100%), which slowly solidified. A colourless crystalline solid, m.p. $128-132^{\circ}$, was obtained by recrystallisation from carbon tetrachloride-chloroform.

IR, table 2; NMR, table 22.

1,5-diamino-3-methyl-3-azabicyclo (3.3.1) non-6-ene (21)

A solution of the aminoolefin (1a), (1.135 gm.; 5mM), in dry THF (60 ml.) was treated carefully with a suspension of lithium aluminium hydride (2.5 gm.) in dry THF (20 ml.), and the mixture refluxed for 4 hr. (overnight reflux gave a lower yield, whereas reduction at room temperature was incomplete). To the cooled reaction mixture was added moist ethanol, and the filtrate from suction filtration was evaporated and extracted with chloroform. The lithium salts were washed with hot chloroform, and the combined organic extracts washed, dried, and evaporated, yielding (21) as a volatile yellow oil

(526 mg.; 53%). Routine IR (Liquid film) 3350 broad (NH), 3050 (=C-H), 2800 (NMe), 1610 cm^{-1} broad (NH def.) and no NO_2 str. Distillation afforded, with 75% loss, a pale yellow oil, b.p. ca. 100-180°/ 0.3 mm., which darkened on standing to form material insoluble in chloroform. The NMR spectrum was not easily assignable, but contained 7.69s, 7.79s (ca. 4H, possibly amine H). TLC analysis showed extensive tailing, even in amine buffer solvents. Its picrate was dark yellow, m.p. ca. 130-140°, and too insoluble to be recrystallised. Attempts to isolate a solid diacetyl derivative were also unsuccessful.

Attempted bis-deamination of triamine (21)

a) The triamine (21), (140 mg.; 0.84 mM), dissolved in acetic acid (1 ml.) was treated portionwise over 1 hr. at 0° with sodium nitrite (280 mg.). Stirring was continued at room temperature overnight. Sodium nitrite (70 mg.) was then added, the mixture stirred for 1 hr., diluted with water (1 ml.), and extracted with chloroform. The product, a dark yellow gum (19 mg.), had an IR spectrum similar to that of (21), with additional absorption at 1730 (acetate C=O) and 1550 cm^{-1} . TLC for this, and all other deamination products, was unhelpful, persistent tailing being observed. The acidic aqueous layer was poured on to cold saturated sodium hydroxide solution (4 ml.), and extracted with chloroform, yielding more of the above material (29 mg.). Similar products were obtained

after heating for 1 hr. after each addition of sodium nitrite, or by leaving the reaction mixture stirring for 4 days before extraction.

b) A solution of (21), (53 mg.), in acetic acid (1 ml.) and water (2 ml.) was treated over 1 hr. with sodium nitrite (30 mg.), the mixture stirred for 90 min., and warmed for 1 hr. on the steam bath. Extraction as in (a) gave a very impure product similar to those from (a).

1,5-dinitro-3,6-dimethyl-3-azabicyclo (3.3.1)nonan-7B-ol (26)

To a suspension of sodium borohydride (78 mg.; 15/8 mM plus ca. 10% excess) in dry THF (5 ml.), and the aminoolefin (1b), (1.205 gm.; 5 mM), was added dropwise over 30 min., with stirring and in a nitrogen atmosphere, boron trifluoride etherate (357 mg.; 2.5 mM). The mixture was stirred under nitrogen for 20 hr. (2 hr. stirring led to much lower yields), and water (2 ml.) was carefully added, followed by saturated sodium hydroxide solution (3N; 1 ml.) and aqueous hydrogen peroxide (30%; 1 ml.). After being stirred for 40 hr., the solution was extracted with chloroform, and the organic extracts washed, dried, and evaporated, leaving a brown crystalline solid (1.210 gm.). The product contained much starting material, together with the more polar alcohol (IR, TLC), separation being achieved by preparative TLC (thickness 0.6 mm., eluant: light petroleum/30% EtOAc, each plate run three times). The more polar

band contained crystalline (26), (85 mg. from 720 mg. product; 11%), m.p. 96-97.5° (colourless crystals from aqueous ethanol). IR, table 2; NMR, table 22.

Jones oxidation of (26)

The alcohol (26), (10 mg.) was treated in the usual way with excess Jones reagent, yielding a mixture of three components, all more polar than (26). Routine IR showed much weaker hydroxyl absorption (3500 cm^{-1}), a carbonyl doublet at 1720 and 1680 cm^{-1} , and a nitro band at 1555 cm^{-1} .

1,5-dinitro-3-methyl-7-amido-3-azabicyclo (3.3.1) non-6-ene (23)

The reaction mixture from 3,5-dinitrobenzamide (2 gm.) was stirred for 2 hr. after acidification, suction-filtered, and the filtrate extracted with chloroform (4 X). The filtered solid was washed several times with water and dried, affording reasonably pure (23), (1.18 gm.). The chloroform extract was washed, dried, and evaporated, leaving pale yellow crystalline material (482 mg.), largely insoluble in chloroform, identical to the filtered solid (IR). The total yield was 1.702 gm. (67%), m.p. 201-203° (colourless plates from ethanol).

Found: C, 44.53; H, 4.98; N, 20.62. $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_5$ requires C, 44.45; H, 5.22; N, 20.73.

IR, table 1; NMR, table 21; mass spectrum, table 12.

1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) nonan-7-one (23)

(a) from amide (2d)

To a stirred solution of amide (2d), (3.24 gm.; 12mM), in THF (35 ml.) and methanol (25 ml.), cooled by an ice-salt bath, was added over 15 min. sodium hypochlorite solution ^{41,57} (0.798N; 18 ml.), the temperature being kept below -5°. The mixture was allowed to warm to room temperature, stirred for 30 min., heated to 55-65° for 10 min., and dilute hydrochloric acid (6N; 2 ml.) was carefully added. The resultant clear red solution was refluxed for 30 min. on the steam bath, cooled, basified with solid potassium carbonate, filtered, and extracted with chloroform (6 X). The chloroform extract was washed and dried. Removal of solvents afforded a partially solid red oil, which contained starting amide (IR, TLC), together with five other compounds, two of which were predominant (TLC). The amide was removed by several filtrations from chloroform solution, followed by evaporation of solvent. This yielded amide (203 mg.) and a clear red oil (2.688 gm.), further purified by thorough extraction with hot carbon tetrachloride to a paler, more mobile oil which partially solidified. The ketone (23) was isolated by preparative TLC (thickness 1 mm., eluant: light petroleum /50% EtOAc). From the least polar band was obtained crude crystalline (23), (336 mg.; 12.3% based on consumed amide), m.p. 120-121° (colourless needles from carbon tetrachloride).

Found: C, 44.23; H, 5.45; N, 17.22. $C_9H_{13}N_3O_5$ requires C, 44.45; H, 5.39; N, 17.28.

It formed neither a picrate nor a dibenzylidene derivative.

IR, table 6, 7; NMR, table 24.

(b) from vinyl ether (2e) (See p. 129)

1,5-dinitro-3-methyl-3-azabicyclo (3.3.1) nonan-7 α -ol (33)

A solution of aminoketone (23), (73 mg.; 0.3 mM), in ethanol (10 ml.) was treated portionwise with sodium borohydride (28 mg.), and stirred for 8 hr. Brine was then added, and the mixture extracted with chloroform. The organic layer was washed, dried, and evaporated, leaving (33) as a colourless crystalline solid (67 mg.; 91%), m.p. 159.5-162.5° (colourless needles from ethanol-carbon tetrachloride).

Found: C, 43.91; H, 6.02; N, 17.00. $C_9H_{15}N_3O_5$ requires C, 44.08; H, 6.17; N, 17.13.

From its IR and NMR spectra (tables 2 and 22 respectively), (33) was shown to have an endo hydroxyl group.

1,5-dinitro-3-ethyl-3-azabicyclo (3.3.1) non-6-ene (34)

m-Dinitrobenzene (2 gm.) was reduced by sodium borohydride in the usual way (see preparation of (2b)). A mixture of ethylamine (70% aqueous solution; 5 ml.) in water (5 ml.), formaldehyde (9 ml.) and water (9 ml.) was then added. After being

stirred for 3 hr., the mixture was acidified with acetic acid (8 ml.), stirred for a further 90 min., and extracted with chloroform. The organic extract was washed (brine), and extracted with dilute hydrochloric acid, the acidic extract basified with solid potassium carbonate and extracted with chloroform. On removal of solvent, there remained a red-brown oil (1.18 gm.; 41%). Extraction with hot ethanol, cooling, filtration of precipitated black gum, re-cooling, and filtration afforded (34) as a pale yellow crystalline solid, m.p. 41-42° after further recrystallisation from ethanol. In later runs, pure (34) was extracted more easily by hot petrol 40-60°. Solubility in ethanol increased with purity, and the analytical sample was obtained by recrystallisation from light petroleum (60-80°, then 40-60°).

Found: C, 49.78; H, 6.48; N, 17.60; $C_{10}H_{15}N_3O_4$ requires C, 49.79; H, 6.27; N, 17.42.

IR, table 4; NMR, table 16; mass spectrum, table 13.

Picrate, m.p. 153-159° (2 X ethanol/EtOAc).

1,5-dinitro-3-benzyl-3-azabicyclo (3.3.1) non-6-ene (35)

The reduction of m-dinitrobenzene (2 gm.) by sodium borohydride, and addition of ice-water was carried out as in the preparation of (2b). Benzylamine (3 ml.) in water (6 ml.), formaldehyde (9 ml.) and water (9 ml.) were added together, and the

mixture stirred for 2 hr. Acetic acid (9 ml.) was then added, and after being stirred for 1 hr., the solution was filtered and extracted with chloroform. The procedure used in the preparation of (34) yielded a dark red oil (443 mg.; 12%). Attempted recrystallisations from a variety of solvents were unsuccessful. Picrate, after recrystallisation from ethanol, had m.p. ca. 134-144° (some "sweating" commencing at ca. 125°).

Found: C, 47.45; H, 4.04; N, 15.80. $C_{21}H_{20}N_6O_{11}$ requires C, 47.37; H, 3.79; N, 15.78.

IR (of ~~35~~), table 4; NMR (of picrate), table 6.

1,5-dinitro-3-azabicyclo (3.3.1) non-6-ene (36)

Reduction of m-dinitrobenzene (2 gm.) as in the preparation of (2b), was followed by addition of a mixture containing concentrated ammonia (S.G. 0.88; 9 ml.), formaldehyde (9 ml.), and water (9 ml.), and stirring for 1 hr. On acidification with acetic acid (9 ml.), the colour of the solution changed from dark brown to orange, and a brown oil was precipitated. Stirring for 1 hr. (overnight stirring gave a negligible yield of basic material), extraction with chloroform and isolation as for (34) furnished a dark yellow oil (1.01 gm.; 40%) which partially solidified. Routine IR showed NH absorption and TLC (using an amine buffer solvent, 14% dimethylamine in benzene) showed the presence of two amines. The product was washed with hot ethanol, hot carbon tetrachloride, and cold ethanol (till the washings were colourless),

leaving a straw-coloured solid, m.p. 132-140°, which could not be recrystallised from carbon tetrachloride/chloroform or carbon tetrachloride/methanol. Picrate, m.p. ca. 150-185° (ethanol). Further recrystallisation did not change the m.p. range, which appeared to include two melting points. TLC also indicated the presence of two picrates, but insolubility in common solvents precluded the use of preparative TLC.

IR, table 3; NMR, table 17.

Attempted preparation of 1,5-dinitro-3-phenyl-3-azabicyclo (3.3.1) non-6-ene (37)

Treatment of m-dinitrobenzene (2 gm.) as in the preparation of (35), with aniline instead of benzylamine, yielded a brown oil (340 mg.), containing some aniline (odour, IR spectrum). The product was a mixture of three compounds, the two main ones being less polar than (1a).

Attempted preparation of 1,5-dinitro-3-acetyl-3-azabicyclo (3.3.1) non-6-ene (38)

m-Dinitrobenzene (2 gm.) was reacted as in the preparation of (35), with acetamide (1 gm.) in place of ammonia. Chloroform extraction afforded a red oil (740 mg.), which appeared to contain two components, both more polar than starting material, and tailing considerably (TLC). Its IR spectrum did not indicate the presence of a tertiary amide, and no solid was obtained from a cooled ethanolic extract.

1,5-dinitro-7-carbomethoxy-3-azabicyclo (3.3.1) non-6-ene (39)

Methyl 3,5-dinitrobenzoate (2 gm.), treated as in the preparation of (36), gave a clear green solution on acidification with acetic acid. The chloroform extract was washed, dried, and evaporated. The residue was a viscous pale yellow oil (1.85 gm.; 77%) which slowly crystallised. Washing with hot chloroform, then hot methanol, gave (39) as a colourless powder, further purified by dissolving in hot chloroform, adding carbon tetrachloride and then light petroleum 40-60°, and cooling (using large volumes of solvents). The m.p. was 191.0-192.5°.

Found: C, 44.40; H, 4.66; N, 15.55. $C_{10}H_{13}N_3O_6$ requires C, 44.28; H, 4.83; N, 15.49.

IR, table 3; NMR, table 21.

Hydrogenation of 1,5-dinitro-7-carbomethoxy-3-azabicyclo (3.3.1) non-6-ene (39)

The aminoester (39), (73 mg.), dissolved in acetic acid (5 ml.), was hydrogenated for 7 hr. with Adams' catalyst (40 mg.). Filtration and evaporation of solvent left a colourless viscous gum, too insoluble for TLC analysis. IR showed ester and nitro group absorption, and a peak at 1635 cm^{-1} replacing one at 1655 cm^{-1} (C=C) in (39).

Attempted cyclisation of the hydrogenation product

A mull of the hydrogenation product (of uncertain constitution) was heated for 20 min. at 180-200°. Some darkening was

observed, and the resultant highly viscous material showed IR absorption at 1640 and 1560 cm^{-1} , the broad carbonyl peak having disappeared. Removal of nujol by washing with chloroform left a hard brown gum, the insolubility of which precluded TLC or further spectroscopic analysis.

1,5-dinitro-7-amido-3-azabicyclo (3.3.1) non-6-ene (42)

After treatment with the Mannich reagents used in the preparation of (36), 3,5-dinitrobenzamide (2 gm.) gave a solution which was stirred for 15 min., acidified with acetic acid (9 ml.), and stirred for 30 min. Filtration afforded (42) as a solid which was washed with water and dried (570 mg.). The filtrate was extracted with chloroform (2 X) and ethyl acetate (2 X), and the organic extracts washed and dried. Removal of solvents yielded an orange oil which slowly solidified. Recrystallisation (1 X ethanol) gave more (42) as a pale yellow solid (140 mg.; total yield 29%). The solids were washed thoroughly with hot chloroform and hot methanol, giving a colourless powder, m.p. 234-235°, totally insoluble in all common solvents.

Found: C, 42.28; H, 4.67; N, 22.02. $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_5$ requires
C, 42.19; H, 4.72; N, 21.87.
IR, table 3; NMR, table 21.

Attempted preparation of 1,5-dinitro-3-ethyl-7-amido-3-azabicyclo (3.3.1) non-6-ene (43)

Following the procedure for the preparation of (34), 3,5-

dinitrobenzamide (2 gm.) yielded a viscous orange oil (ca. 100 mg.), after extracting the basified acidic extract with chloroform, followed by ethyl acetate. A crude red solid was obtained on filtering the reaction mixture prior to extraction. Although these products may have contained the desired amide (IR spectra), purification by recrystallisation was unsuccessful.

Attempted preparation of 1,5-dinitro-3-benzyl-7-amido-3-azabicyclo (3.3.1) non-6-ene (44)

Following the procedure for the preparation of (35), the reaction mixture from 3,5-dinitrobenzamide (2 gm.), stirred for 20 min. before and after acidification, was extracted with chloroform, then with ethyl acetate, to yield a yellow oil (1.15 gm.). Although the product had the expected IR spectrum, TLC analysis showed it to be a mixture of several components. Recrystallisation from ethanol was unsuccessful.

1,5-dinitro-3-methyl-7-methoxy-3-azabicyclo (3.3.1) non-6-ene (2e)

A solution of 3,5-dinitroaniso⁴²le (2 gm.; prepared from 1,3,5-trinitrobenzene) in THF (30 ml.) formamide (20 ml.) and methanol (10 ml.) was treated in the usual way (with cautious addition of acetic acid to control the violent effervescence in this case, followed by stirring for 30 min.) to yield (2e) as a red oil, solidifying on standing (1.70 gm.; 66%). Recrystallisation from ethanol was difficult (large wastage, also material sensitive to heat),

and gave colourless crystals, m.p. 110-111°, which slowly yellowed on exposure to light.

Found: C,46.81; H,5.79; N,16.39. $C_{10}H_{15}N_3O_5$ requires C,46.69; H,5.88; N,16.33.

IR, table 1; NMR, table 5.

Hydrolysis of (2e) to the aminoketone (23)

The vinyl ether (2e), (182 mg.), dissolved in dilute hydrochloric acid (10 ml.) was heated for 2 hr. on the steam bath. The cooled solution was basified with dilute aqueous sodium carbonate and extracted with chloroform. The organic extracts were washed, dried, and evaporated to yield a crystalline solid (172 mg.; 100%) identical with (23) prepared from the amide (2d).

1,5-dinitro-7-methoxy-3-azabicyclo (3.3.1) non-6-ene (48)

Reduction of 3,5-dinitroanisole (2 gm.), dissolved in THF (30 ml.) and ethanol (15 ml.), by sodium borohydride (2 gm.), was followed by addition of ice-water (50 ml.) and 8 ml. each of ammonia, formaldehyde, and water. After being stirred for 30 min., acetic acid (8 ml.) was carefully added, with stirring for a further 30 min. Filtration and extraction of the filtrate with chloroform gave a red oil containing some solid material, which was removed by several filtrations and evaporations of the chloroform solution. This material was not the desired product (IR spectrum). The red oil was acid-washed in the usual way to extract basic material (720 mg.) which

slowly solidified. Routine IR showed the presence of NH, C=C and NO₂ groups, and also NCH₃. It consisted of two compounds, the less polar predominating. Separation was accomplished by preparative TLC (thickness 1mm., eluant: light petroleum /30% EtOAc). The main (less polar) band yielded 363 mg. crystalline solid, identical to the N-methyl analogue (2e) of the desired product (IR, TLC, m.p. after recrystallisation). From the other band was obtained (48) as a pale yellow oil (160 mg.; 6.5%), which did not solidify. IR, table 3; NMR, table 23.

1,5-dinitro-3-ethyl-7-methoxy -3-azabicyclo (3.3.1)non-6-ene (49)

3,5-dinitroanisole (2 gm.) when treated as in the preparation of (34), afforded a red oil (1.79 gm.), which consisted of one predominant compound, and several more polar ones (TLC). By means of preparative TLC (thickness 1mm., eluant: light petroleum /20% EtOAc, each plate run twice), the major constituent (49) was obtained as a pale yellow oil (283 mg.; 10.3%). IR, table 4; NMR, table 23. Picrate, m.p. ca. 143-158° (3 X EtOH).

1,5-dinitro-3-benzyl-7-methoxy -3-azabicyclo (3.3.1) non-6-ene (50)

Following the procedure used for the preparation of (35), 3,5-dinitroanisole (1 gm.) formed a red oil (1.315 gm.), consisting of two compounds, the less polar one predominating. Separation by preparative TLC (as for (49)) gave (50) as a pale yellow oil (407 mg.; 24%).

IR, table 4; NMR, table 23. Picrate, n.p. ca. 140-152° (2 X EtOH).

1,5-dinitro-3-azabicyclo (3.3.1) nonan-7-one (45)

The dinitrovinyl ether (48), (100 ng.), was hydrolysed as in the preparation of (23), forming a yellow oil (73 ng.; 70%), which crystallised on cooling. M.p. range was wide, final m.p. being ca. 170°. Recrystallisation was however unsuccessful. IR, table 6,7.

1,5-dinitro-3-ethyl-3-azabicyclo (3.3.1) nonan-7-one (46)

Hydrolysis (as for (48)) of (49), (100 ng.), afforded (46) as a colourless crystalline solid (71 mg.; 75%), m.p. 121-123° (colourless needles from carbon tetrachloride).

Found: C, 46.71; H, 5.83; N, 16.31. $C_{10}H_{15}N_3O_5$ requires C, 46.69; H, 5.88; N, 16.33.

IR, table 6,7; NMR, table 24.

1,5-dinitro-3-benzyl-3-azabicyclo (3.3.1) nonan-7-one (47)

The product (47) from hydrolysis (as for (48)) of (50), (100 ng.) was a solid, which precipitated from the aqueous acidic solution on cooling, and was totally extractable without basification. (67 ng.; 70%). m.p. 155-157° (colourless needles from carbon tetrachloride).

Found: C, 56.65; H, 4.81; N, 13.26. $C_{15}H_{17}N_3O_5$ requires C, 56.42; H, 5.37; N, 13.16.

IR, table 67 NMR, table 24.

Attempted preparation of 1,5-dinitro-2,4-diphenyl-3-methyl-3-azabicyclo (3.3.1) non-6-ene

m-Dinitrobenzene (2 gm.) was reduced in the usual way. Benzaldehyde (2.5 gm.), then methylamine (33% in EtOH; 8 ml.), was added with cooling. After being stirred for 42 hr., the opaque red solution was acidified with acetic acid (8 ml.). Extraction of basic material gave a brown oil (680 mg.), a complex mixture of ca. six components (TLC).

Attempted preparation of 1,5-dinitro-2,3,4-trimethyl-3-azabicyclo (3.3.1) non-6-ene

m-Dinitrobenzene (2 gm.), after reduction, was treated with a mixture of acetaldehyde (4 ml.) in water (4 ml.), methylamine (33% aqueous; 8 ml.) and water (8 ml.). After being stirred for 2 hr., the mixture was acidified with acetic acid (8 ml.), stirred for 1 hr., and filtered. Basic material was extracted as a viscous red-black gum (162 mg.), consisting mainly of one impure compound (TLC). It could not be obtained solid, nor could a picrate be prepared.

Attempted preparation of the azatricyclododecane (51)

Reduction of m-dinitrobenzene (2 gm.) with sodium borohydride (1.5 gm.) was followed by treatment with a mixture of glutaraldehyde (25% aqueous solution; 10 ml.), methylamine (10 ml.), and water (10 ml.). The mixture was stirred for 1 hr., acidified with acetic acid (10 ml.),

and stirred for a further 1 hr. Extraction of basic material yielded a brown oil (22 mg.), which was not further investigated.

Attempted preparation of the azatricyclododecane (52)

Under similar conditions, methyl 3,5-dinitrobenzoate (2 gm.) formed a brown gum (115 mg.). Routine IR showed the presence of ester and nitro groups, but TLC indicated a complex mixture (much of the material remaining on the baseline).

Attempted condensations between the disodium salt (53) and electrophiles, aiming at 1,5-dinitrobicyclo (3.3.1) non-2-enes

a) ACROLEIN

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To a suspension of the salt (53) in the solvent mixture was added dropwise at 0° acrolein (equimolar amount), with or without the addition of base. The mixture was stirred for several (usually 2-4) hours, acidified with acetic acid, and extracted with chloroform.

In all cases, the products (red or black oils) had peaks in the IR due to C=O, NO₂ and sometimes OH, indicating that some condensation had occurred. Large amounts of starting material were recovered in the absence of base, but in the presence of hydroxide or ethoxide, these amounts were greatly decreased. Also present were two or three other components (TLC), e.g., after addition of 1:1 acrolein: ethoxide, and stirring for 65 hr., no starting material was present, but the crude product was a complex mixture. No purer product was obtained by isolating the solid salt (53), and (under the last-

mentioned conditions), stirring for 13 hr.

Distillation of the product was ineffective, due to charring.

b) ACRYLONITRILE

Addition of acrylonitrile (under conditions described for acrolein) yielded after ether extraction a dark red oil. Routine IR showed nitrile, nitro, and carbonyl absorption, and TLC analysis indicated a mixture of three components. Distillation afforded with large loss an orange oil, b.p. ca. $30^{\circ}/0.03$ mm., with nitrile, but no nitro absorption in the IR, i.e. decomposition had occurred.

c) PHENYL VINYL KETONE (PVK)

The salt (53) was filtered and washed with dry ethanol. A solution of PVK (equimolar amount; obtained by distillation of the Mannich base hydrochloride) in dry ether was added dropwise over 10 min. under nitrogen to a stirred suspension of (53) in dry ethanol at -70° . The mixture was stirred for 1 hr., aliquots being removed after 5, 20, and 40 min. After addition to ice and acidification with dilute tartaric acid, extraction with chloroform gave products with identical highly complex thin layer chromatograms. IR contained peaks at 1680 (broad; C=C and/or PhCO), 1600, 1580 (ar. C=C) and 1550 (NO_2) cm^{-1} . Unsuccessful efforts were made to obtain solid products.

1-methyl-2,4-dinitrocyclohex-1-ene³³ (54)

2,4-dinitrotoluene (4 gm.) reduced by sodium borohydride

(4 gm.) and the mixture acidified with 10% tartaric acid, afforded a mobile red oil (3.45 gm.). Routine IR showed a weak peak at 1680 (C=C), and a broad one at 1560 cm^{-1} (NO_2). The corresponding peaks in the starting material were at 1605 and 1540 cm^{-1} . TLC analysis however indicated the presence of three components (two compounds predominating, possibly double bond isomers). The product became lighter in colour on distillation (b.p. ca. 116°/0.1 mm.; Lit. 75°/0.1 mm., then analysed), the yield being 1.90 gm. (Lit. yield not quoted). IR then showed a strong peak at 1685 cm^{-1} (C=C), but the material was of unchanged composition (TLC). After several days, the IR peak at 1685 cm^{-1} was of much weaker intensity, i.e., the material was unstable and reverting to its undistilled state.

Attempted preparation of 1-carboxy-3,5-dinitrocyclohex-1-ene (56)

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Under the conditions described in the reduction of the 2,4-dinitro acid, 3,5-dinitrobenzoic acid (2.5 gm.) formed a red oil, consisting mainly of possibly a single acid (IR, TLC in acid buffer solvent). Extraction with saturated aqueous bicarbonate solution gave a dark red acidic liquid, which did not solidify, and which appeared to be unstable (darkened, with decreasing solubility in ether). Cf. the analogous 2,4-dinitroacid, m.p. 153° (CH_2Cl_2), and analysed. ³³

Attempted preparation of 1-carbethoxy-3,5-dinitrocyclohex-1-ene (57)

Ethyl 3,5-dinitrobenzoate (2 gm.) was reduced as in the

preparation of (2b). Dilution with ice-water (200 ml.), acidification with 10% tartaric acid (50 ml.) and stirring for 12 hr., was followed by extraction with methylene chloride. The organic extracts were washed with saturated sodium bicarbonate solution, leaving neutral material as a dark red oil. Routine IR: 1725, 1550, 750 cm^{-1} (starting material 1725, 1630, 1550, 730 cm^{-1}). TLC analysis showed the product to be a mixture of several compounds, considerable streaking occurring on chromatograms.

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1-carbethoxy-3-methyl-3-azabicyclo (3.3.1) nonan-9-one (58)

2-carbethoxy cyclohexanone (6.0 gm.; 0.035 M) afforded a basic pale brown oil (4.6 gm.; Lit. 7.2 gm.), which had the expected IR spectrum, but consisted of about four components (TLC). Treatment of the product with ethanolic picric acid gave a brown gum. Purification was accomplished by preparative TLC (thickness 1 mm., eluant: light petroleum/25% EtOAc). Extraction of the first main layer above the baseline yielded reasonably pure (58) (one main spot TLC). The recovery was 25-35%, representing a yield of 15-21%. Mass spectrum ($P=225 \text{ m/e}$) showed peaks at 224 ($P-1$), 196 ($P-29$, loss of C_2H_5), and 180 ($P-45$, loss of OEt) m/e . IR, table 5; NMR, table 25.

Attempted preparation of 1-carbethoxy-3-methyl-3-azabicyclo (3.2.1) octan-8-one (56)

Using the procedure for the preparation of (58),

2-carbethoxycyclopentanone (5.46 gm.; 0.035 M) formed a pale-brown basic fraction (1.17 gm.). TLC analysis showed four compounds to be present, the two main ones having R_f values similar to (58). Separation by preparative TLC (as for (58)), and examination of the IR spectra of the two compounds, showed however that neither was the desired compound (66).

1-hydroxymethyl-3-methyl-3-azabicyclo (3.3.1) nonan-9-ol (61)

A suspension of lithium aluminium hydride (1.0 gm.; 30 mM; 3M excess) in dry THF (15 ml.) was added carefully dropwise to a solution of ketoester (58), (2.25 gm.; 10 mM), in dry THF (35 ml.), and the mixture refluxed for 15 hr. Remaining LAH was destroyed by cautiously adding moist ethanol. A large volume of brine was added, and the mixture extracted with chloroform. The organic extracts were washed, dried, and evaporated to leave (61) as a viscous pale yellow oil (1.52 gm.; 82%). A sample was distilled to yield a viscous colourless liquid, b.p. ca. 125-130°/1mm., which slowly solidified. Several recrystallisations from light petroleum 60-80°, then light petroleum 60-80°/carbon tetrachloride, afforded a colourless solid, m.p. 105-131° (C₉ epimers). Further recrystallisation did not raise the m.p., and satisfactory analytical figures were not obtained. The mass spectrum had a parent ion at $P=185$ m/e.

IR, table 8; NMR, table 26.

1-tosyloxymethyl-6-methylbicyclo (4.3.1)-dec-7-en-10-ol (71)

The diol (68), ⁶¹ (980 mg.; 5mM), dissolved in dry pyridine (4 ml.) was treated with a solution of tosyl chloride (970 mg.; 5mM plus slight excess) in dry pyridine (4 ml.). The mixture was kept at 0° for 3 days, and extracted as in the preparation of (43), except for a acidification with dilute hydrochloric acid prior to chloroform extraction. The product, a yellow oil (1728 mg.; 99%) partially solidified, and consisted (TLC) of two compounds (C₁₀ epimers). Separation by preparative TLC (thickness 0.75 mm., eluant: light petroleum/25% EtOAc) gave the more polar epimer as a yellow oil (408 mg.), and the less polar epimer as a yellow oil (1083 mg.) which solidified, m.p. 130-137° (light petroleum 60-80°/carbon tetrachloride). IR, table 9; NMR, table 27.

1-tosyloxymethyl-5-methylbicyclo (3.3.1) non-3-en-9-ol (72) ⁶²

The diol (69), (prepared by reduction ^{61, 62} of the corresponding ketoester; 98%, Lit. 92%) (910 mg.; 5 mM), under the conditions described in the preparation of (71), afforded a semi-solid pale yellow oil, containing both C₉ epimers (TLC). Preparative TLC (thickness 0.75 mm., eluant: light petroleum/15% EtOAc, each plate run twice), yielded the less polar epimer as a crystalline solid (817 mg.), m.p. 71-72° (light petroleum 60-80°).

Found: C, 64.77; H, 7.44. C₁₈H₂₄O₄S requires C, 64.26; H, 7.19.

The more polar component (140 mg.), which did not solidify, contained a trace of its epimer (TLC). The yield of pure (72) was 64% (Lit. epimeric mixture had m.p. 65-67°, yield 90%).
IR, table 9; NMR, table 27.

1-tosyloxymethyl-6-methylbicyclo (4.3.1) decan-10-ol (73)

The diol (70),⁶¹ (434 mg.), formed on tosylation a pale yellow semi-solid oil, which when washed with light petroleum 60-80° became a colourless crystalline solid (440 mg.), m.p. 106-5°-108° (light petroleum 60-80°). This solid appeared to be a single compound (TLC).

Found: C, 64.88; H, 7.87. C₁₉H₂₈O₄S requires C, 64.75; H, 8.00. The washings contained a yellow oil (240 mg.), consisting of (73) and a trace of diol (TLC). The yield was >73% (assuming only half of petrol-soluble material to be (73)).

IR, table 9; NMR, table 27.

1-tosyloxymethyl-3-methyl-3-azabicyclo (3.3.1) nonan-9-ol (62)

A distilled sample of the diol (61), (370 mg.; 2 mM), dissolved in dry pyridine (1 ml.) was treated with a solution of tosyl chloride (390 mg.; in slight excess of 2 mM) in dry pyridine. After being left at 0° for 3 days, the mixture was added to ice, and extracted with chloroform. The chloroform layer was washed, dried, and evaporated to yield a brown oil (279 mg.). TLC analysis

indicated the presence of a trace of diol (even after the reaction was left for 7 days at 0°), a less polar compound (62), and a least polar compound. Separation by preparative TLC (thickness 1 mm., eluant: EtOAc) afforded (62) as a brown oil (68 mg.; 10%) which did not solidify. IR, table 9; NMR, table 27.

1-tosyloxymethyl-6-methylbicyclo (4.3.1) dec-7-en-10-one (74)

The less polar epimer of (71), (393 mg.), on treatment with excess Jones reagent afforded a yellow oil (337 mg.), consisting of two compounds with very similar R_f values (TLC). Separation was achieved by preparative TLC (thickness 0.75 mm., eluant: light petroleum /7.5% EtOAc, each plate run six times), affording the less polar material (74) as a crystalline solid (224 mg.; 57%), definitely only one compound (TLC), with m.p. 82.5-83.5° (light petroleum 60-80°). Found: C, 65.22; H, 6.91. C₁₉H₂₄O₄S requires C, 65.50; H, 6.94. IR, table 10; NMR, table 28.

The more polar component (41 mg.), also a crystalline solid, possessed the CH₂OTs group (IR, NMR) but lacked the C=C (NMR) and C=O (IR) groups. It was not further investigated.

Under similar conditions, the more polar epimer of (71) formed a product that contained ca. 20% acidic material. The neutral product was a complex mixture (TLC). These products were not further examined.

1-tosyloxymethyl-5-methylbicyclo (3.3.1) non-3-on-9-one (75)

Both epimers of (72), when oxidised by Jones reagent, yielded identical products (IR, TLC, m.p.) (yields: more polar epimer 89%, less polar, 93%). M.p. 65-68° (light petroleum 60-80°). TLC chromatograms, run five times in light petroleum /10% EtOAc, showed that two compounds of almost identical R_f were present. These might be Δ^2 double bond isomers, formed by the acidic oxidation conditions (this was not however observed in the case of (74)). Found: C, 64.60; H, 6.63. $C_{19}H_{22}O_4$ S requires C, 64.65; H, 6.63. IR, table10; NMR, table28.

1-tosyloxymethyl-6-methylbicyclo (4.3.1) decan-10-one (76)

The monotosylate (73), (23 mg.), when treated with excess Jones reagent, furnished a colourless oil (227 mg.; 99%). A sample separated from trace impurities by preparative TLC (thickness 0.25 mm., eluant: light petroleum /10% EtOAc) solidified, and had m.p. 74-76° (light petroleum 60-80°). Mass spectrum ($P=350$ m/e) had peaks at 195 (loss of Ts, 155), 179 (loss of OTs, 171) and 178 (loss of TsOH, 172) m/e.

IR, table10; NMR, table28.

1-tosyloxymethyl-3-methyl-3-azabicyclo (3.3.1) nonan-9-one (63)

A solution of the monotosylate (62), (380 mg.) in acetone (10 ml.) was treated with excess Jones reagent with stirring at 0°.

After 30 min., excess methanol was added, then excess brine, and the mixture extracted with chloroform. The organic layer was washed, dried, and the solvents removed, leaving a brown oil (288 mg.).

Neutralisation of the acidic aqueous layer with saturated aqueous sodium carbonate, followed by chloroform extraction, yielded further product (21 mg.). The total yield was 304 mg. (81%). Samples for spectral data were freed from more polar impurities by preparative TLC (thickness 0.25 mm., eluant: light petroleum/15% EtOAc) which furnished (63) as a brown gum which did not solidify.

IR, table 10; NMR, table 28.

Treatment of the ketotosylates (74), (75) and (76) with strong base

a) Sodium ethoxide

A solution of the ketotosylate in dry ethanol was stirred under reflux with a solution of sodium ethoxide in dry ethanol. Water was added to the cooled solution, and the acidified (dilute HCl) mixture was extracted with ether. The organic extract was washed with saturated aqueous sodium bicarbonate, brine, and dried.

The ketotosylate (76), (150 mg.) in dry ethanol (9 ml.) was treated 16 hr. as above with sodium (15 mg.) in dry ethanol (5 ml.). The product (90 mg.) contained unchanged (76), a more polar component (predominating), and a less polar component. IR showed strong hydroxyl and carbonyl absorption at 3450 and 1710, 1695 cm^{-1} respectively. More prolonged treatment (50 hr.) afforded similar material. Separation

by preparative TLC (thickness 0.25 mm., eluant: light petroleum /30% EtOAc) yielded the most polar constituent (25 mg.) as a colourless oil. IR (CCl₄): 3630 (free OH), 3515 broad (bonded OH), doublet at 1697, 1686 (C=O). The evidence indicated structure (77). Treatment of this material with tosyl chloride in pyridine furnished a product containing unchanged (77) and a less polar compound with a R_f value similar to that of (76).

The ketotosylate (75) when treated as above for 50 hr., remained almost totally unchanged. When refluxed for 4 days, however, the product consisted of starting material, one less polar, and two more polar compounds. Here again, IR showed strong hydroxyl and carbonyl absorption at 3500 and 1710 cm.⁻¹, respectively, as well as absorption due to (75).

b) Potassium t-butoxide

The procedure used was similar to that in (a), with potassium in t-butanol instead of sodium in ethanol.

The ketotosylate (76) after 19 hr. afforded a mixture of compounds, containing no (76), but three less polar components and one more polar. Since the IR spectrum (3500s, hydroxyl, and 1700s, carbonyl) was similar to that of (77), it appeared that the most polar constituent was the ketol (77).

Similar IR absorption was exhibited by the product from (74)

after 14 hr. reflux. This consisted of ca. three compounds, two being more polar than (74), and the less polar of these predominating. By analogy with (76), the latter was probably the ketol (79).

The product after 17 hr. from (75) contained equal amounts of acidic (probably two acids) and neutral material. The latter was a highly complex mixture, with IR absorption similar to that quoted above.

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SUMMARY

P.R.D. THESIS

Part I : Synthetic approaches to allohimachalol

2-(γ -formylbutyl)-2,6,6-trimethylcycloheptanone was synthesised in six steps from tetrahydroeucarvone. Attempts to effect aldol cyclisation to 1,5,5,8-tetramethylbicyclo (4.4.1) undec-7-en-11-one, which has already been related to the naturally occurring sesquiterpene alcohol allohimachalol, were unsuccessful.

Other approaches afforded a variety of compounds, in particular, a number of bicyclo (4.3.1) decanes derived from 1,5,5-trimethyl-8-oxabicyclo (5.4.0) undec-6-en-9-one.

Part II : Studies in the 3-azabicyclo (3.3.1)nonane system

The reported procedure for the syntheses of a small number of 6-substituted 1,5-dinitro-3-methyl-3-azabicyclo (3.3.1)non-6-enes was extended to provide a wide range of 6- and 7-substituted analogues, the structures of which have been rigorously proved by chemical and spectroscopic methods.

Initial difficulty in assigning certain NMR signals of these compounds led to a study of the NMR shifts of protons α and β to the nitrogen atom in simple amines and amine picrates. Some correlation between structure and magnitude of shift was observed.

The scope of the reaction sequence leading to these compounds

was thoroughly investigated, and a number of 3-unsubstituted, 3-ethyl, and 3-benzyl analogues prepared. In particular, this made available several 3-substituted 1,5-dinitro-3-azabicyclo (3.3.1)nonan-7-ones, IR studies of which established the absence of interaction between the amine and carbonyl functions.

Evidence was presented confirming reported findings of the chair-chair conformation of the 3-azabicyclo (3.3.1)nonane system.